Official Title: PaTHway Trial: A Phase 3, Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel Group Trial, with an Open-Label Extension, Investigating the Safety, Tolerability and Efficacy of TransCon PTH Administered Subcutaneously Daily in Adults with Hypoparathyroidism

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CLINICAL STUDY PROTOCOL

Product Name:	TransCon PTH (Palopegteriparatide)
Protocol Number:	TCP-304
IND Number:	133469
EUDRACT Number:	2020-003380-26
Phase:	3
Protocol Title:	**PaTHway TRIAL:** A Phase 3, Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel Group Trial, with an Open-Label Extension, Investigating the Safety, Tolerability and Efficacy of TransCon PTH Administered Subcutaneously Daily in Adults with Hypoparathyroidism
Protocol Date:	V1.0, 23 SEP 2020 V2.0, 16 MAR 2021 V3.0, 10 JUN 2021 V4.0, 03 AUG 2021 V5.0, 20 DEC 2021 V6.0, 13 DEC 2022 V7.0, 25 May 2023
Protocol Version:	V7.0
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SUMMARY OF CHANGES – VERSION 6.0 TO VERSION 7.0

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

This amendment to the protocol is being issued to add precaution in case of use of digoxin during the open-label extension period based on authority feedback and to add administrative updates.

Note that added text is highlighted in bold character. When the only change consists of a deletion or the replacement of a single term, the deleted or replaced text is marked with a horizontal line (~~strikethrough~~), leaving the deleted/replaced text legible.

Section(s)	Description of Change (s)	Brief Rationale
Title Page	Remove PPD as Medical Monitor, Add PPD as Medical Monitor, Update PPD title PPD **~~MD~~** PPD ~~Ascendis Pharma, Inc.~~ ~~1000 Page Mill Road, Palo Alto, California 94304, United States~~ ~~Phone:~~ PPD ~~Cell:~~ PPD ~~email:~~ PPD PPD **, MD** PPD PPD Ascendis Pharma, Inc. 1000 Page Mill Road, Palo Alto, California 94304, United States Phone: PPD email: PPD PPD **, MD** PPD	Administrative changes
Section 9.6.1 Dose changes and Treatment Interruptions	• Persistent ***severe hypercalcemia*** with albumin-corrected serum calcium ~~>~~≥12.0 mg/dL[4] for >7 days despite: Footnote 4: Thresholds for albumin-corrected serum calcium:~~>~~ ≥12.0 mg/dL (~~>~~≥3.00 mmol/L), or ionized calcium:~~>~~ ≥1.50 mmol/L	Correction for consistency

Section(s)	Description of Change (s)	Brief Rationale
Section 9.9.2 Prohibited Therapies	Added following precaution: **TransCon PTH increases calcium, and therefore concomitant use with digoxin (which has a narrow therapeutic index) may predispose patients to digitalis toxicity if hypercalcemia develops. When TransCon PTH is used concomitantly with digoxin, measure serum calcium and digoxin levels, and monitor for signs and symptoms of digoxin toxicity.**	The use of digoxin is permitted in the open label extension period if clinically indicated and should be used with caution as hypercalcemia may predispose the subject to digoxin toxicity. The protocol is updated with the precaution based on authority feedback to protocol version 6.0
Section 12.1.5 Special Situation	Examples of special situations include and should all be captured in the eCRF: • Pregnancy • Breastfeeding • Overdose • Drug abuse • Misuse • ~~Off label use~~ • Occupational exposure • Lack of therapeutic efficacy • Medication error	Subjects participating in the trial will not be treated off-label

SUMMARY OF CHANGES – VERSION 5.0 TO VERSION 6.0

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

This amendment to the protocol is being issued to clarify the use of prohibited medications during the open-label extension period, to add an efficacy endpoint for extension period and to provide clarification on the trial.

Note that added text is highlighted in bold character. When the only change consists of a deletion or the replacement of a single term, the deleted or replaced text is marked with a horizontal line (~~strikethrough~~), leaving the deleted/replaced text legible.

Section(s)	Description of Change (s)	Brief Rationale
Title Page	Update address of Ascendis Pharma, Inc	Administrative Change
Title Page	Add PPD and Remove PPD as Medical Monitor	Administrative Change
Section 9.5.2.1. SoC Dose Adjustments during Blinded Treatment Period Section 11.14. Laboratory Assessments	SoC adjustments should be made **preferably** within 48 hours of blood collection. Investigators must be able to receive local laboratory results within a time frame sufficent to allow instructions to subjects on dose adjustments **preferably** within 48 hours of blood collection	Clarification of time frame for titration
Section 9.9.2. Prohibited Therapies	The following therapies are prohibited **during the blinded phase**: ~~throughout the trial~~ **For the open-label extension period, these medications are allowed only if deemed necessary by the investigator for patient safety considerations. Use of bisphosphonates or denosumab requires consultation with the Medical Monitor to determine potential impact on integrity of relevant endpoints.**	Clarification of use of these medications during open-label extension period
Section 12.4.2. Recording Procedures for All Adverse Events	**AEs will be documented at the maximum intensity experienced. If a previously recorded and closed AE or condition recorded as part of medical history increases in severity or frequency, it will be recorded as a new AE.**	Language updated to clarify collection of AEs
Section 12.5.2. Reporting	All SAEs, AESIs, and Special Situations (including follow-up information) must be reported ~~to e-mail: ascendis@pharmalex.com~~ ~~OR~~ ~~fax: 003497 620 4402~~**using the Safety report form or the Pregnancy report form provided. A completed Safety report form / Pregnancy report form must be uploaded to the Safety Reporting Portal at:**	Updated safety reporting process from email/fax to online safety reporting portal to be compliant to data privacy regulation

	Safety.ascendispharma.com **Specific instructions regarding completion of the form and reporting details are provided on the Safety report form.**	
Synopsis Section 15.2.1.2.2. Other Secondary Efficacy Endpoints	The ~~primary and~~ key secondary efficacy endpoints **and the following efficacy endpoint** will be~~ measured~~ **evaluated** at predefined timepoints during the Extension Period. • **The proportion of subjects that meet the following criteria:** – **Albumin-adjusted sCa measured within the normal range (8.3-10.6 mg/dL); and** – **Independence from active vitamin D (i.e., standing dose of active vitamin D equal to zero on the day prior to the Week 52 visit or other visits of interest); and** – **Independence from therapeutic doses of calcium (i.e., standing dose of elemental calcium ≤ 600 mg on the day prior to the Week 52 visit or other visits of interest).**	Add an efficacy endpoint for Extension Period
Synopsis Section 15.3. Statistical Analysis	**All efficacy endpoints will be summarized descriptively in Extension Period analysis.**	Specify how analysis will be done for efficacy endpoints for Extension Period

SUMMARY OF CHANGES – VERSION 4.0 TO VERSION 5.0

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

This amendment to the protocol is being issued to address comments and recommendation from the Food and Drug Administration (FDA).

Note that added text is highlighted in bold character. When the only change consists of a deletion or the replacement of a single term, the deleted or replaced text is marked with a horizontal line (~~strikethrough~~), leaving the deleted/replaced text legible.

Section(s)	Description of Change (s)	Brief Rationale
Synopsis Section 15.2.1.1 Primary Efficacy Endpoints	• Independence from therapeutic doses of calcium (i.e., taking calcium supplements ≤600 mg/day). This dose of calcium ≤600 mg/day in the form of tablets, powder, liquid suspension, or transdermal patch is considered as "supplemental" to meeting recommended daily intake for general health, as opposed to a "therapeutic" dose to treat hypoparathyroidism*** **and** • **No increase in prescribed study drug within 4 weeks prior to Week 26 visit**** **** **Dose decrease permitted for safety reasons**	CCI
Synopsis Section 15.2.1.2.1 Key Secondary Efficacy Endpoints	Change from baseline at 26 weeks of treatment: • HPES symptom – ~~Total~~ **Physical domain** score • **HPES Symptom –Cognitive domain score** • HPES Impact - **Physical functioning domain**~~Total~~ score • **HPES Impact – Daily life domain score** • 36-Item Short Form Survey (SF-36) Physical ~~component~~ **functioning subscale** score ~~• SF-36 Mental component score~~ ~~In addition, HPES domains scores (Physical, Cognitive, Physical Functioning, Daily Life, Psychological Well-being, Social life and Relationships) and SF-36 subscale scores (Physical Functioning, Role Limitations due to Physical Health Problems, Bodily Pain, General Health, Vitality, Social Functioning, Role Limitations due to Emotional Problems and Mental Health) will be analyzed.~~	CCI
Synopsis Section 15.2.1.2.2 Other Secondary Efficacy Endpoints	• **HPES: HPES Impact domain scores (Psychological Well-being and Social life and Relationships) and HPES Symptom and Impact total scores** • **SF-36 subscale scores (Role Limitations due to Physical Health Problems, Bodily Pain, General Health, Vitality, Social Functioning, Role Limitations due to Emotional Problems, and Mental Health) and SF-36 component scores (Physical component score and Mental component score)**	CCI

Section(s)	Description of Change (s)	Brief Rationale
Synopsis Section 15.3 Statistical Analysis	~~Gatekeeping testing procedure~~ **Sequential testing** will be applied to control the family-wise type-1 error rate for the primary and key secondary endpoints. Details will be specified in the SAP. In general, continuous endpoints during Blinded Treatment Period will be analyzed using ANCOVA model **with unequal covariance**. The model will include the change from baseline for the endpoint of interest as a response variable, treatment assignment and etiology of hypoparathyroidism as fixed factor and baseline value of the endpoint will be entered as a covariate, unless otherwise specified in the SAP. The **key secondary** PRO efficacy endpoints will be analyzed as continuous and in terms of change from baseline using the described ANCOVA model **with multiple imputation for missing post-baseline assessments**.	CCI [redacted]
Appendix 2. Titration Algorithm Footnote 5	~~Through Week 52: e~~**C**Check sCa within 7-14 days after any changes in study drug dose; standing calcium, standing vitamin D doses; or sCa outside the normal range. A scheduled visit or LV within 7-14 days meets this requirement. When scheduled study visits occur less frequently (e.g. 13 weeks apart) then an ULV should be pursued. ~~After Week 52 of the trial check sCa within 7-31 days after any changes in study drug dose.~~	CCI [redacted]
Appendix 2. Titration Algorithm Note	At all times during the trial, subjects with symptoms of hypocalcemia may take PRN doses of calcium (preferred) and/or active vitamin D, and/or do an ULV visit to measure sCa. **Subjects with symptoms of hypercalcemia may hold doses of study drug for 1 day and/or do an ULV to measure sCa. An ULV must be performed within 7 days of a PRN supplement dose or a held dose**. ~~An ULV must be performed within 7 days of a PRN supplement dose.~~ ~~At all times during the trial, subjects with **symptoms** of hypercalcemia may **hold doses of study drug** for 1 day and/or do an ULV to **measure sCa**. An ULV must be performed within 7 days of a held dose.~~ **If due to symptoms >2 PRN doses of SoC are taken or >2 doses of SoC and/or study drug are held within those 7 days, an ULV is required within 2 days of the third PRN or held dose.**	CCI [redacted]

SUMMARY OF CHANGES - VERSION 3.0 TO VERSION 4.0

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

Note that added text is highlighted in bold character. When the only change consists of a deletion or the replacement of a single term, the deleted or replaced text is marked with a horizontal line (~~strikethrough~~), leaving the deleted/replaced text legible.

Section(s)	Description of Change (s)	Brief Rationale
Section 9.6.1 Dose changes and Treatment Interruptions	• maximum protocol permitted dose of study drug • ~~study drug dose ≥30 µg/day~~	Administrative correction. Updated to reflect the maximum dose of study drug in the protocol
Section 11.9.4 36-Item Short-Form Survey	The 36-Item Short-Form Survey (SF-36) V2 Health Survey **(1-week recall)** is a multipurpose short-form health survey with 36 questions that yields an eight-scale profile of functional health and general well-being, as well as two psychometrically based physical and mental health summary measures and a preference-based health utility index.	CCI [redacted]
Synopsis Section 15.2.1.1 Primary Efficacy endpoints	At 26 weeks of treatment, the proportion of subjects with: • Albumin-adjusted sCa **measured within 4 weeks prior to and on the Week 26 visit are** within the normal range (8.3-10.6mg/dL) *; and • Independence from active vitamin D** and • Independence from therapeutic doses of calcium (i.e., taking calcium supplements ≤600 mg/day). This dose of calcium ≤600 mg/day in the form of tablets, powder, liquid suspension, or transdermal patch is considered as "supplemental" to meeting recommended daily intake for general health, as opposed to a "therapeutic" dose to treat hypoparathyroidism*** *** Except for at the Week 26 visit, confirmation that an albumin-adjusted sCa is "abnormal" requires 2 consecutive results outside the normal range within 4 weeks prior to the Week 26 visit.** ****Independence from active vitamin D will be defined as a daily standing dose equal to zero on all days AND use of any PRN vitamin D ≤7 days within 4 weeks prior to the Week 26 visit.** *****Independence from therapeutic calcium will be defined as average daily standing dose ≤600 mg AND use of PRN doses on ≤7 days within 4 weeks prior to the Week 26 visit.**	CCI [redacted]

Section(s)	Description of Change (s)	Brief Rationale
	* ~~Daily calcium and active vitamin D doses are calculated as the sum of standing and PRN doses on a calendar day. Independence from therapeutic calcium is defined as daily elemental calcium dose ≤600 mg on the calendar day of and day prior to the week 26 visit. Independence from active vitamin D is defined as receiving no active vitamin D in the same 2-day period.~~	
Synopsis Section 15.2.1.2 Secondary efficacy endpoints	**Change from baseline at 26 weeks of treatment:** ~~At 26 weeks of treatment:~~ • ~~Change from baseline in HPES~~ • ~~Change from baseline in 36-Item Short Form Survey (SF-36)~~ • **HPES Symptom - Total score** • **HPES Impact - Total score** • **36-Item Short Form Survey (SF-36) Physical component score** • **SF-36 Mental component score** **In addition, HPES domains scores (Physical, Cognitive, Physical Functioning, Daily Life, Psychological Well-being, Social life and Relationships) and SF-36 subscale scores (Physical Functioning, Role Limitations due to Physical Health Problems, Bodily Pain, General Health, Vitality, Social Functioning, Role Limitations due to Emotional Problems and Mental Health) will be analyzed.**	CCI [redacted]
Section 15.3 Statistical Analysis	**Subjects with no Week 26 albumin-adjusted sCa OR with >25% (i.e., >7 days) missing diary data of active vitamin D or calcium during the 4 weeks will be considered as non-responders.** ~~Subjects who have missing data on one or more of the criteria for the primary endpoint at time of the analysis will be considered as non-responders~~	Clarification of handling of missing data
Appendix 2	Decrease calcium supplements by ≥1500 mg/day[6]	Clarification of PI's discretion to continue calcium supplementation to meet nutritional requirements if clinically warranted
Appendix 2 Footnote 5	**Through Week 52**: Check sCa within **7-14** ~~31~~ days after any changes in study drug dose; **standing calcium, standing vitamin D doses; or sCa outside the normal range.** A scheduled visit or LV within **7-14** ~~31~~ days meets this requirement. When scheduled study visits occur less frequently e.g. 13 weeks apart) then an ULV should be pursued. **After**	CCI [redacted]

Section(s)	Description of Change (s)	Brief Rationale
	Week 52 of the trial check sCa within 7-31 days after any changes in study drug dose.	
Appendix 2 Notes	**Adjustments of study drug, calcium and/or active vitamin D will be made per the titration algorithm based on the results of the most recent laboratory results whether scheduled or unscheduled. When central and local calcium values are obtained concurrently, local values should be used to guide titration.**	Clarification regarding use of titration algorithm after scheduled and unscheduled laboratory visit calcium values
Appendix 3	Weekly diary ~~activation~~ **dispensing**	Updated to reflect the use of paper weekly diary

SUMMARY OF CHANGES - VERSION 2.0 TO VERSION 3.0

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

This amendment to the protocol is being issued to provide clarification on the trial. Comments from the National Security Agency of Medicine and Health Products (ANSM) were also taken into consideration.

Note that added text is highlighted in bold character. When the only change consists of a deletion or the replacement of a single term, the deleted or replaced text is marked with a horizontal line (~~strikethrough~~), leaving the deleted/replaced text legible.

Section(s)	Description of Change (s)	Brief Rationale
Synopsis 8.1.1 Inclusion Criteria 8.1.2 Exclusion Criteria	Standardized units as milli-international units per liter (mIU/L) ~~mIU/mL~~ **mIU/L**	Correction. Updated to denote TSH units as milli-international units per liter (mIU/L).
Synopsis 8.1.1 Inclusion Criteria	**** Excluding individuals receiving PTH-like drugs within 12 weeks of the screening visit, who need only demonstrate a stable requirement for elemental calcium and active vitamin D above minimum thresholds for 5 weeks prior to the screening visit.***	Prior PTH treatment considered equivalent to requirements for high dose SoC supplementation.
Synopsis 8.1.2 Exclusion Criteria	Note: Male subjects must use a condom, or his female partner of childbearing potential must use an effective form of contraception **(as per CTFG definition)** ~~as described in Appendix 1~~, from the beginning of screening to the last trial visit	Clarification regarding definition of effective contraception use in male participants with female partners of childbearing age.
Synopsis	~~Sequential testing~~ **Gatekeeping procedure** will be applied to control the ~~family wise type 1 error rate between the~~ **multiplicity for the** primary and key secondary endpoint. ~~Additional multiplicity control will be applied for the key secondary endpoints.~~	Update multiplicity control method
11.5 Electrocardiogram Appendix 3. Schedule of Events	Standard 12-lead ECG, **which includes QT interval and Heart Rate,** will be recorded when the subject is in a resting state, prior to blood collection if performed at the same visit. ~~A historical ECG performed within the 6 months prior to Screening is acceptable if the report includes QT interval and Heart Rate. For the UK only: A study specific ECG reporting heart rate and QT interval must be performed at screening.~~	As per ANSM request
11.12 Subject Diary	**Paper diary might be used as back-up solution.**	Back-up solution

Section(s)	Description of Change (s)	Brief Rationale
11.8 Dietary Calcium Questionnaire	Update of hyperlink **https://www.osteoporosis.foundation/educational-hub/topic/calcium-calculator**	Correction
11.10 Local Tolerability Assessment	**(See section 12.4.3.4 for ISR reporting)** ~~An ISR is defined as a reaction at the site of administration that is deemed abnormal from those ordinarily observed in SC injections (including pain intensity, pruritus, swelling, induration, ulceration, lipoatrophy, lipodystrophy, and infection). Asymptomatic erythema is not considered an ISR but can be captured as an AE of erythema. In general, occasional mild pain or bleeding is expected with all daily SC injections, and should not be captured as AEs unless the frequency or severity is greater than expected or normally seen with SC injections.~~	Clarification of rationale and intentions for reporting and AE determination of injection site reactions.
12.1.1 Adverse Event	An AE is ~~any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational medicinal product (IMP) or other protocol-imposed intervention, regardless of attribution. This includes the following:~~ An AE is **defined as any untoward medical occurrence in a clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with the treatment. An Adverse event can therefore be any of the following:**	Clarification of definitions, in accordance with ICH E6 GCP and ICH E2A guidance
12.1.2 Serious Adverse Events	**An SAE is any untoward medical occurrence at any dose that meets any of the following criteria:** ~~An AE should be classified as an SAE if any of the following criteria are met:~~	Clarification of definitions, in accordance with ICH E6 GCP and ICH E2A guidance
12.4.3.1 Abnormal Laboratory Values	**Abnormal serum calcium values will not be considered AEs unless associated with a sign or symptom*** Results in a medical intervention (e.g., potassium supplementation for ~~hypoccalmia~~ **hypokalemia** or a change in concomitant therapy. **** Abnormal serum calcium values - whether or not associated with titration of study drug, calcium, or active vitamin D doses - will not be considered AEs unless associated with a sign or symptom. Serum calcium is a pharmacodynamic marker of study drug therapy and thus used to guide titration of study drug, calcium, and active vitamin D doses (per Appendix 2).***	Clarification of rationale and intentions for AE reporting due to calcium abnormalities. These do not constitute AEs unless symptomatic – to remain consistent with protocol V1.0.

Section(s)	Description of Change (s)	Brief Rationale
12.4.3.3 Diagnosis vs. Signs and Symptoms	If known at the time of reporting, a diagnosis should be reported rather than individual signs and symptoms (e.g. record only ~~hypercalcemia~~ **heart failure** rather than ~~abdominal pain, nausea, polyuria,~~ **dyspnea, orthopnea** and ~~high serum calcium~~ **extremity edema**).	Clarification
12.4.3.4 Injection Site Reactions	12.4.3.4 Injection Related Site Reactions ~~Each sign or symptoms will be recorded as a separate AE on the AE eCRF.~~ ~~Local reaction~~ **ISRs that occur during or after study drug administration and that are judged to be related to study drug injection are deemed to be AEs. These AEs** ~~at the site of injection administration~~ should be captured as **a** unified diagnosis ~~rather than as individual signs and symptoms~~ on the AE eCRF (e.g. ~~adverse event reporting~~as an **"**injection site reaction**"** rather than capturing **"**injection site bleeding**"** ~~or~~ **and "**injection site induration**"** as separate adverse events). **The diagnosis is at the discretion of the investigator. Signs, symptoms, and features of the injection site reaction should be recorded on a dedicated corresponding eCRF.**	Clarification of rationale and intentions for reporting and AE determination of injection site reactions.
12.5 Safety Reporting Requirements	12.5 Safety Reporting Requirements ~~**12.5 Serious adverse events (SAE) and suspected unexpected serious adverse reactions (SUSAR)**~~	Heading updated for reader clarity
15.1 General	~~Data from clinical assessments will be summarized using descriptive statistics. Numerical variables will be summarized by mean, median, standard deviation (SD), standard error (SE), minimum, and maximum while categorical variables will be summarized by counts and proportions.~~ ~~The primary analysis will use the Cochran-Mantel-Haenszel (CMH) test stratified by etiology of hypoparathyroidism (post-surgical vs other) to compare the proportion of subjects meeting the listed criteria of the primary endpoint (responders vs. non-responders) in the TransCon PTH vs. placebo groups. Sequential testing will be applied to control the family-wise type-1 error rate between the primary and key secondary endpoints. Additional multiplicity control will be applied for the key secondary endpoints. Details will be specified in the SAP.~~	Redundant paragraph deleted
15.3 Statistical Analysis	• Analysis: CMH test stratified by etiology of hypoparathyroidism **(post-surgical vs. other)** is the primary analysis method and will be used to	Update multiplicity control method

Section(s)	Description of Change (s)	Brief Rationale
	compare the proportion of subjects meeting the listed criteria of the primary endpoint (responders vs. non-responders) in the TransCon PTH vs. placebo groups ~~Sensitivity analyses be performed, and the details will be provided in SAP.~~ **Gatekeeping testing procedure will be applied to control the family-wise type-1 error rate for the primary and key secondary endpoints. Details will be specified in the SAP.** The model will include the change from baseline for the endpoint of interest as a response variable, treatment assignment **and etiology of hypoparathyroidism** as fixed factor and baseline value of the endpoint will be entered as a covariate, unless otherwise specified in the SAP.	
Appendix 1. Contraception	Methods of contraception with a failure rate of more than 1% per year with consistent adherence are not permitted **for female participants of childbearing potential.**	Clarification
Appendix 3. Schedule of Events	Footnote 5: COAs: PRO measures must be completed by the subject without assistance and prior to conducting any clinical assessments or supplement dose adjustments. **On visit 6, 9 and 10/ET, additional** CCI **needs to be completed by the subject.** The CGI-S should be completed by the investigator after all clinical assessments are completed.	Change in CCI collection format
Appendix 3. Schedule of Events	Footnote 17: ~~A single~~ **Repeat** TSH may be performed during the Screening Period if the baseline measurement is out of the allowable range.	Clarification

SUMMARY OF CHANGES - VERSION 1.0 TO VERSION 2.0

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

This amendment to the protocol is being issued to address comments and recommendation from the Food and Drug Administration (FDA) and provide clarification on the trial. Comments from the Federal Institute for Drugs and Medical Devices (BfArM), Medicine and Healthcare products Regulatory Agency (MHRA) and National Security Agency of Medicine and Health Products (ANSM) were also taken into consideration.

Note that added text is highlighted in bold character. When the only change consists of a deletion or the replacement of a single term, the deleted or replaced text is marked with a horizontal line (~~strikethrough~~), leaving the deleted/replaced text legible.

Section(s)	Description of Change (s)	Brief Rationale
Title page	Change title from PPD to PPD for PPD Added PPD **MD as Medical Monitor** PPD ~~, MD~~ as Medical Monitor	Implemented as an Administrative amendment
Throughout the protocol and added in Section 4.0. List of Abbreviations and Definitions	Change "~~rescue~~" to "**PRN**" (as needed)	Clarification of abbreviation and definition
Section 4.0. List of Abbreviations and Definitions	Revised to capture current protocol status **CMH: Cochran-Mantel-Haenszel** **DMC: Data Monitoring Committee** ~~ISC – Independent Safety Committee~~	Administrative change
Section 5.1.3. Current Standard Therapy for Hypoparathyriodism	Table 1 deleted	Administrative change
Throughout the protocol	Please refer to the current version of the TransCon PTH Investigator's Brochure, for example, ***Section 4 – Nonclinical Studies*** for a full summary ~~discussion~~ of the nonclinical data	To include reference to the specific sections in the IB
Section 5.3. Clinical Experience	Figure 3 shows a dose-dependent increase in Free PTH, ~~with a half-life of ~60 hours, resulting in an infusion-like profile in the lower half of the normal range at approximate steady-state (after the 10th daily dose)~~, with a low peak-to-trough ratio of ~1.27 to 1.55 over 24 hours. **Phase 1 data demonstrate that the effective half-life of Free PTH released from the prodrug is ~60 hours, with Free PTH approaching steady-state by Day 8 after dosing. This is further supported by sparse PK sampling performed in the Phase 2 trial (TransCon PTH TCP-201).** The normal physiologic range for intact	Introductory section was revised to capture the most updated information on TransCon PTH

Section(s)	Description of Change (s)	Brief Rationale
	PTH(1-84) is 10-65 pg/mL; as PTH(1-34) and PTH(1-33) comprise about 40% of the molecular mass of the intact hormone, the calculated normal range is about 4-26 pg/mL. A total of 59 male and female subjects with HP of at least 26 weeks duration treated with a stable dose of ≥ 0.25 µg BID active vitamin D (or ≥ 1.0 µg/day of alfacalcidol) and ≥400 mg BID calcium for at least 12 weeks prior to Screening were randomized 1:1:1:1 to TransCon PTH 15, 18 or 21 µg/day or to placebo for 4 weeks, followed by an **ongoing** open-label extension for an additional 12 months. **Preliminary data up to 26 weeks of follow up are presently available.** **Analysis of 26 week data from the Phase 2 open label extension confirm these findings, with 91% of participants requiring no vitamin D and ≤500 mg/d elemental calcium. Participants required TransCon PTH doses between 6 and 39 µg/day. No TEAEs related to abnormal serum calcium have required urgent medical attention. No TEAEs have resulted in discontinuation of study drug, withdrawal from the trial or death. There have been no SUSARs as of February 2021. A single participant opted to withdraw consent from the Phase 2 trial in open label Extension Period due to the requirements for contraception.**	
Synopsis Section 6.2. Secondary Objectives	Secondary Objectives: To assess the treatment effect of daily TransCon PTH on pharmacodynamic markers (including sCa ~~and urine calcium [uCa]~~) To assess the treatment effect of daily TransCon PTH on serum phosphate (sP), serum calcium x phosphate product (CxP) (albumin adjusted sCa x sP product)~~,~~ **and** serum magnesium (sMg)~~, urine phosphate (uP) and urine creatinine clearance~~)	Secondary objectives have been adjusted to reflect the endpoints.
Synopsis Section 7.2. Overall Trial Design and Plan	**Randomization will be stratified by etiology of hypoparathyroidism (post-surgical vs other).**	CCI [redacted]
Synopsis Section 7.2. Overall Trial Design and Plan incl. Figure 7 Section 10.1. Trial Duration Appendix 3. Schedule of Events	Blinded Treatment Period (study drug~~-stable with~~ **and** SoC optimization): 26 weeks ~~Titration Period: up to 10 weeks~~ ~~Individualized Dosing Period: up to 16 weeks~~ Deleted Section 10.1.4. and 10.1.5.	Clarification to no longer distinguish between titration and individualized dosing in the Blinded Treatment Period

Section(s)	Description of Change (s)	Brief Rationale
Section 7.2 Overall Trial Design and Plan	~~Subsequently, at every clinic visit (every 2 weeks) up to and including Visit 6 in the Blinded Titration Period, subjects~~ **Study drug, calcium and active vitamin D** will be titrated **according to the Titration Algorithm (Appendix 2) on each occasion serum calcium is measured.** ~~to their optimal TransCon PTH/placebo dose. Starting at Visit 6, all subjects are expected to remain on a stable dose of TransCon PTH or corresponding placebo.~~	Clarification
Section 7.2. Overall Trial Design and Plan Figure 7	Added a footnote ****Target Week for visits between V16 and V26: See Appendix 3 Extension Period**	Clarification
Synopsis 8.1.1. Inclusion Criteria	No.2 Subjects with postsurgical chronic HP, or auto-immune, genetic, or idiopathic HP for at least 26 weeks. Diagnosis of HP is established based on a history of hypocalcemia in the setting of inappropriately low serum PTH levels. **(Hypocalcemia is defined as a value below the reference range for normal at the performing laboratory. Inappropriately low serum PTH levels are defined as at or below the median value of the reference range for normal at the performing laboratory while the concomitant serum calcium is low. If specific lab results at the time of original diagnosis are not available, as historical diagnosis affirming these two components is adequate for inclusion)**	Clarification on hypocalcemia was added to Inclusion Criteria No.2
	No 4. Optimization of supplements prior to randomization to achieve the target serum levels of: • 25(OH) vitamin D levels of 20-80 ng/mL (49-200 nmol/L) and • Magnesium level in the normal range, or just below the normal range i.e.: ≥1.3 mg/dL (0.53 mmol/L) and • Albumin-adjusted or ionized sCa level in the normal range, or *just below the normal range, i.e.: – Albumin-adjusted sCa 7.8-10.6 mg/dL (or 1.95-2.64 mmol/L) – Ionized sCa 4.40-5.29 mg/dL (or 1.10-1.32 mmol/L) ***Just below the normal range implies the numerical range of 7.8-8.2 mg/dL (or 1.95-2.06 mmol/L) for albumin-adjusted sCa and the**	Inclusion No.4 was updated to define "just below normal range" in bullet 3

Section(s)	Description of Change (s)	Brief Rationale
	numerical range of 4.40-4.636 mg/dL (or 1.10-1.159 mmol/L) for ionized sCa.	
	No. 13 **For France only: The subject is obligated to be affiliated with, or beneficiary of a social security system or assimilated**.	Updated to reflect a local French requirement
Synopsis Section 8.1.2. Exclusion criteria	No. 2 Any disease that might affect calcium metabolism or calcium-phosphate homeostasis or PTH levels other than HP, such as active hyperthyroidism; Paget disease of bone; severe hypomagnesemia; type 1 diabetes mellitus or poorly controlled type 2 diabetes mellitus (HbA1C >9%, documented HbA1C result drawn within 12 weeks prior to Screening is acceptable); severe and chronic liver, or renal disease; Cushing syndrome; multiple myeloma; active pancreatitis; malnutrition; rickets; recent prolonged immobility; active malignancy (other than low-risk well differentiated thyroid cancer or ~~basal cell~~ **non-melanoma** skin cancer); active hyperparathyroidism; parathyroid carcinoma within 5 years prior to Screening; acromegaly; or multiple endocrine neoplasia types 1 and 2 No. 11 Pregnant or lactating women Note: Acceptable **highly** effective contraception (see Appendix 1) is required for sexually active women of childbearing potential during the trial and for 2 weeks after the last dose of study drug, and pregnancy testing will be performed throughout the trial. Sexually active women of childbearing potential who are unwilling to use acceptable **highly** effective contraception are excluded from the trial	Clarification
Section 9.3. Selection of Trial Doses	**Old text** **~~The 4-week blinded treatment period of the Phase 2 trial (TransCon PTH TCP-201) with fixed doing of TransCon PTH (15, 18, and 21 µg/day) demonstrated that a dose of 18 µg/day was both effective and well-tolerated, with less hypercalcemia compared to a dose of 21 µg/day and without meaningful hypocalcemia. The Phase 2 trial is ongoing as an open-label extension and overall, based on the preliminary data, the safety profile of 18 µg/day appears to be similar compared to 15 µg/day. During the open-label extension period the dose distribution across subjects has been approximately 6-30 µg/day, titrated to achieve normocalcemia. The~~**	Trial dose section was revised to capture the most updated information on TransCon PTH doses

Section(s)	Description of Change (s)	Brief Rationale
	~~**preliminary data shows no safety concern on TransCon PTH doses <15µg/day or >21µg/day (doses below and above, respectively, the fixed doses of the 4-week blinded treatment period) with no meaningful difference in adverse events (AE) including the AEs related to hypo- or hypercalcemia. Therefore, the starting dose for the Blinded Treatment Period this trial will be 18 µg/day, followed by titration to 6-60 µg/day to ideally achieve normocalcemia and independence from conventional therapy.**~~ **New text** **The 4-week blinded treatment period of the Phase 2 trial - with fixed dosing of TransCon PTH 15, 18, and 21 µg/day - demonstrated that a dose of 18 µg/day was both effective and well-tolerated, with less hypercalcemia compared to a dose of 21 µg/day and without meaningful hypocalcemia. Preliminary data from the open label extension of the Phase 2 trial as of February 2021 demonstrates comparable safety profiles at doses of both 15 and 18 µg/day. The dose distribution during the open label extension has been 6-39 µg/day, titrated to achieve normocalcemia. Phase 2 data demonstrates no meaningful difference in AEs, including those related to hypo- or hypercalcemia, on TransCon PTH doses <15µg/day or >21µg/day. 5-10% of participants are anticipated to require doses >30µg/d to achieve normocalcemia in the present trial. Therefore, the starting dose for the Blinded Treatment Period will be 18 µg/day, followed by titration to 6-60 µg/day to achieve normocalcemia and independence from conventional therapy.**	
Synopsis Section 9.4.2. Treatment Assignment During Open-Label Extension Period	At Visit 10 **(Week 26)**, subjects will be assigned to open-label treatment as follows:	Administrative change
Section 9.5.2.1. SoC Dose Adjustments during Blinded Treatment Period	Subsequently, active vitamin D and/or calcium doses should be titrated as per Appendix 2. **The target vitamin D range during treatment phases of this trial is 30-80 ng/mL**	Clarification of maintenance range
Section 9.5.2.2. Study Drug Dose Adjustments During	Added **Serum calcium results from local laboratory analysis will be used to guide titration of study**	Administrative change

Section(s)	Description of Change (s)	Brief Rationale
Blinded Treatment Period	**drug. Central laboratory results will be definitive for data analysis.**	
Section 9.5.3.1. SoC Dose Adjustments during Extension Period	Added **Start the new SoC regimen:** • **On the day *of* Visit 10 for those subjects who are still taking active vitamin D at the time of Visit 10** • **On the day *after* Visit 10 for those subjects who are off active vitamin D and taking study drug ≥30 µg/day at Visit 10**	Clarification of start of the new SoC regimen at Visit 10
Section 9.6. Study Drug Dose Changes, Interruptions or Stopping	9.6.1. Dose changes and ~~Possible Stopping~~**Treatment Interruptions** ~~A discussion between t~~The investigator ~~and medical monitor~~ will ~~occur to~~ determine dose changes and/or study drug holding/stopping for the following situations Footnote 2 Thresholds for albumin-corrected serum calcium: <7.0 mg/dL (~~>~~<1.75 mmol/L), or ionized calcium: <0.95 mmol/L	Title adjusted to reflect the content in the section better Deleted medical monitor to make it clear that the investigator is responsible for all trial-related medical decisions Corrected typo in footnote 2
Section 9.6.2. Required Stopping	Pregnancy~~, unless the benefit exceeds the perceived risks~~ **Ascendis medical monitors will immediately notify the Data Monitoring Committee (DMC) and Ascendis pharmacovigilance of any such events for evaluation of potential broader safety concerns**	Updated to clarify that pregnancy must result in permanent discontinuation of study drug
Section 9.9.1. Required HP Therapies	Subjects may also be on cholecalciferol (vitamin D3) and magnesium supplements as part of their HP treatment or to achieve the recommended daily allowance (RDA), as **needed to maintain target ranges of each. The 25 (OH) vitamin D target range is 30-80 ng/mL during** ~~trial participation.~~**treatment phases of the trial**. ~~long as doses are expected to remain stable throughout the trial.~~ **Subjects should receive calcium supplementation in the form of calcium citrate in case of concomitant use of proton pump inhibitors or anti-acid therapies.**	Clarification of maintenance range
Section 9.9.2. Prohibited Therapies	The following therapies are prohibited throughout the trial: • PTH therapies other than TransCon PTH	Clarification to guide the investigator without a requirement

Section(s)	Description of Change (s)	Brief Rationale
	• Thiazide or loop diuretics~~, unless otherwise agreed with the Medical Monitor~~ • Phosphate binders (other than calcium supplements) • Digoxin, lithium, methotrexate • Systemic corticosteroids (other than as replacement therapy). Short course use of steroids (≤2 weeks/year) ≤40mg/day is permitted • Bisphosphonates • Denosumab • Biotin >30 µg/day ~~If the administration of a prohibited concomitant medication becomes necessary any time after randomization, contact the Medical Monitor.~~	to discuss with the medical monitor
Section 10.1. Trial Duration Section 11.9.7. Phone Exit Interviews Appendix 3. Schedule of Events	Deleted Section 10.1.4. and 10.1.5. and moved/added In selected **English speaking** countries/**sites**, approximately 2 weeks prior to the final Blinded Treatment Period visit (Visit 10), subjects will be contacted to set up a one-hour phone interview to occur within 2 weeks after the final Blinded Treatment Period visit (Visit 10) to discuss their experience in the trial. In case of subject discontinuation before or at Visit 10, the phone interview will be scheduled to be completed within 2 weeks after the Early Termination Visit. The phone interview will be conducted by an external vendor (see Section 11.9.7).	Clarification that phone interview will only take place in English speaking countries/sites
Section 11.5. Electrocardiogram Appendix 3. Schedule of Events	**For the UK only: A study specific ECG reporting heart rate and QT interval must be performed at screening**	Clarification that UK only accept ECGs performed at screening not historical
Section 11.15.3. Contraception	Irrespectively, acceptable **highly** effective contraception during the trial and for 2 weeks after the last dose of study drug is required for women of childbearing potential if sexually active, and pregnancy testing for women of childbearing potential will be performed throughout the trial. See Appendix 1 for further guidance on acceptable **highly** effective contraception.	Updated to align with Exclusion criteria 11
Section 12. Adverse Event Assessment and Reporting	Section 12 was revised to implement new standard text Minor corrections were done in Section 12.3.1.2. regarding “Outcome Assessment” and its classifications. Added section 12.1.5.	The Adverse Event Assessment and Reporting Section incl. outcome assessment were updated to new

Section(s)	Description of Change (s)	Brief Rationale
	Special Situation **Special situations are non-standard medical conditions that provide valuable information (e.g. clinical, safety) about a medicinal product, even when they do not occur in association with an AE or medical condition. Examples of special situations include and should all be captured in the eCRF:** • **Pregnancy** • **Breastfeeding** • **Overdose** • **Drug abuse** • **Misuse** • **Off label use** • **Occupational exposure** • **Lack of therapeutic efficacy** • **Medication error** **The Medical Monitor will review all safety information on an ongoing basis.** Added section 12.4.3.9. **Product Complaints** **A Product Complaint is defined as any written or oral information received from a complainant that alleges deficiencies related to identity, quality, safety, strength, purity, reliability, durability, effectiveness, or performance of a product after it has been released and distributed to the commercial market or clinical trial.** **In this study, the TransCon PTH delivery system consists of a multi-use cartridge integrated into a device to constitute a pre-filled injection pen which is considered a medical device. The investigator must report all medical device complaints to the Sponsor. The investigator should document as much information as possible including the product batch number and forward the information to the Sponsor immediately (refer to the pharmacy manual for further details). If the medical device results in an adverse event to the study patient, the event must be reported on the AE eCRF and submitted through the EDC system. If the event is serious, the AE eCRF must be completed immediately (i.e., no more than 24 hours after learning of the event), as outlined in Section 12.5.2.**	standard text for alignment across Ascendis Pharma clinical trial

Section(s)	Description of Change (s)	Brief Rationale
Section 13. Safety Monitoring	Replaced with new standard text	Safety monitoring was updated to new standard text for alignment across Ascendis Pharma clinical trial
Synopsis Section 15.1. Statistics – General Section 15.3. Statistical Analysis	The primary analysis will use the ~~Fisher's exact~~**CMH (Cochran-Mantel-Haenszel)** test **stratified by etiology of hypoparathyroidism (post-surgical vs other)** to compare the proportion of subjects meeting the listed criteria of the primary endpoint (responders vs. non-responders) in the TransCon PTH vs. placebo groups. Analysis: ~~Fisher's exact~~**CMH** test **stratified by etiology of hypoparathyroidism** is the primary analysis method and will be used to compare the proportion of subjects meeting the listed criteria of the primary endpoint (responders vs. non-responders) in the TransCon PTH vs. placebo groups Categorical endpoints during Blinded Treatment Period will be analyzed using ~~Fisher's exact~~**CMH** test **stratified by etiology of hypoparathyroidism.**	Updated statistical analysis method Implemented as an administrative amendment
Synopsis Section 15.2.1.1. Primary Efficacy Endpoint	Added text ***Daily calcium and active vitamin D doses are calculated as the sum of standing and PRN doses on a calendar day. Independence from therapeutic calcium is defined as daily elemental calcium dose ≤600 mg on the calendar day of and day prior to the week 26 visit. Independence from active vitamin D is defined as receiving no active vitamin D in the same 2-day period.**	Clarification of the primary endpoint
Synopsis Section 15.2.1.2.1. Key Secondary Efficacy Endpoints	Key Secondary Efficacy Endpoints At 26 weeks of treatment~~, the proportion of subjects with~~: ~~Albumin-adjusted sCa within the normal range (8.3-10.6mg/dL);~~ ~~and~~ ~~Independence from active vitamin D~~ ~~and~~ ~~Independence from therapeutic doses of calcium (i.e., taking calcium supplements ≤600 mg/day)~~ ~~and~~ ~~Normal 24-hour urine calcium excretion (≤250 mg/24h for females, ≤300 mg/24h for males) or ≥ 50% reduction from baseline~~ ~~sP levels at 26 weeks~~ ~~HPES domain scores at 26 weeks~~ • **Change from baseline in HPES** • **Change from baseline in 36-Item Short Form Survey (SF-36)**	CCI [redacted]

Section(s)	Description of Change (s)	Brief Rationale
Synopsis Section 15.2.1.2.2. Other Secondary Efficacy Endpoints	The primary and key secondary efficacy endpoints will be measured at predefined timepoints during the Extension period. The following endpoints will be evaluated ~~after 26 weeks~~ at predefined timepoints during **the** ~~of~~ **Blinded Treatment and** ~~at predefined timepoints during~~ the Extension Period: Calcium and active vitamin D doses ~~every 26 weeks~~ Daily "pill burden" of active vitamin D and calcium (as oral tablets, powder, liquid solutions, liquid suspensions, or transdermal patches) ~~assessed every 26 weeks~~ ~~Normal 24-hour uCa excretion (≤250 mg/24h for females, ≤300 mg/24h for males), or ≥50% reduction from baseline at 52, 104, 156 and 182 weeks~~ sP ~~every 26 weeks~~ Albumin-adjusted sCa x sP product, including proportion of subjects with albumin-adjusted sCa x sP product ≤55 mg^2/dL^2, ≤52 mg^2/dL^2, and ≤44 mg^2/dL^2 ~~every 26 weeks~~ Albumin-adjusted sCa ~~every 26 weeks~~ ~~24-hour uP at 26, 52, 104, 156 and 182 weeks~~ BMD and TBS by DXA ~~at52, 104 and 182 weeks~~ Bone turnover markers (serum P1NP and CTx) ~~at 52, 104 and 182 weeks~~ sMg ~~every 26 weeks~~ ~~SF-36~~ EQ-5D CGI-S	CCI
Synopsis Section 15.2.2. Safety Endpoints	Safety Endpoints The following safety endpoints will be assessed during the Blinded Treatment and Extension Periods: Incidence of AEs, AESI and SAEs ~~24-hour uCa excretion~~ Serum chemistry and hematology~~, and~~ **24-hour** urine chemistry (including urine **calcium and urine** creatinine clearance) **at prespecified timepoints including Week 26** Clinical events of hypo- or hypercalcemia (emergency/urgent care visits and hospitalizations) Injection site tolerability (based on AEs) Evaluation of anti-PTH, anti-TransCon PTH and anti-PEG antibody responses Vital signs	Updated to reflect the change in safety endpoints

Section(s)	Description of Change (s)	Brief Rationale
Section 15.3. Statistical Analysis	Pharmacokinetic Analysis The PK parameters and their statistical evaluation will be included in the Clinical Study Report. PK data will be used to describe plasma concentration at steady-state. Potential impact of any anti-PTH, anti-TransCon PTH and anti-PEG antibodies detected will be included in the evaluation. **The Free PTH results will additionally be added to the population PK analysis.**	Clarification for Free PTH results
Section 16.6. Trial Termination or Completion	**The Sponsor must also terminate the trial prematurely for any of the following reasons:** **Unjustifiable risk and/or toxicity in risk-benefit analysis (occurrence of new adverse events unknown to date in respect of their nature, severity, duration or frequency in relation to the current established safety profile of the study drug)** **New scientific evidence becomes available during the study that could affect the subject's safety**	Premature termination criteria has been specified
Section 17. Ethical and Legal Considerations	Previous Section 17.1. Data Safety Monitoring Committee/Independent Safety Committee updated ~~Independent oversight of this trial may be provided by a data safety monitoring committee/independent safety committee, if deemed appropriate.~~ **17.1. Data Monitoring Committee** **Independent oversight of this trial will be provided by a DMC. Its duty is to regularly review the progress of the trial and assess the accumulating safety data. After each meeting it will advise the Sponsor on the continuing safety of current subjects in the trial and on the continuing validity and scientific merit of the trial. All decisions about the conduct of the trial will rest solely with the Sponsor. The DMC will consist of members, all with experience in clinical studies, and who will operate based on the Charter agreed upon. The Charter will define data content, format, and review frequency. The Sponsor may attend the DMC meetings.**	Clarification
Appendix 1. Contraception	~~Due to the lack of genotoxic or teratogenic or reproductive toxicity with any component of TransCon PTH, acceptable effective contraception are methods that result in a failure rate of more than 1% per year when used consistently and correctly are permitted in this trial. Following the Clinical Trial Facilitation Group recommendations (CTFG 2014), such methods include:~~	Updated to align global requirement for highly effective forms of contraception

Section(s)	Description of Change (s)	Brief Rationale
	~~• Progestogen-only oral hormonal contraception, where inhibition of ovulation is not the primary mode of action~~ ~~• Male or female condom with or without spermicide~~ ~~• Cap, diaphragm or sponge with spermicide~~ ~~Subjects of child-bearing potential can also use h~~ **H**ighly effective contraception **are methods** that can achieve a failure rate of less than 1% per year when used consistently and correctly, following the CTFG 2014 recommendations, such methods include: • Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation: – Oral – Intravaginal – Transdermal • Progestogen-only hormonal contraception associated with inhibition of ovulation: – Oral – Injectable – Implantable • Intrauterine device (IUD) • Intrauterine hormone-releasing system (IUS) • Bilateral tubal occlusion/ligation • Vasectomized partner • Sexual abstinence, defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments • Postmenopausal. A postmenopausal state is defined as no menses for 12 months without an alternative medical cause **Methods of contraception with a failure rate of more than 1% per year with consistent adherence are not permitted**. Periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhoea method (LAM) are not acceptable methods of contraception. ~~Female condoms and male condoms should not be used together.~~	
Appendix 2. Titration Algorithm	[4]**If albumin-adjusted** sCa ≥12.0 mg/dL (3.00 mmol/L) **or ionized calcium ≥1.50 mmol/L**, hold study drug for approximately 2-3 days. Remember to resume study drug therapy afterwards. Also reduce study drug, active vitamin D, or calcium as per algorithm.	Clarification of sCa level and ULV

Section(s)	Description of Change (s)	Brief Rationale
	Notes: At all times during the trial, subjects with symptoms of hyp**o**calcemia may take ~~**rescue**~~ **PRN** doses of calcium (preferred) and/or active vitamin D, and/or do an ULV visit to measure sCa. **An ULV must be performed within 7 days of a PRN supplement dose.** At all times during the trial, subjects with symptoms of hyp**er**calcemia may hold doses of study drug for 1 day and/or do an ULV to measure sCa. **An ULV must be performed within 7 days of a held dose.**	
Appendix 3. Footnote 17	Multiple local laboratory assessments over the approximate 4 weeks of the Screening Period are expected in order to optimize both the albumin-adjusted or ionized sCa to the normal range, as well as normalize the sMg and vitamin D level. **A single repeat TSH may be performed during the Screening Period if the baseline measurement is out of the allowable range.**	Clarification

STATEMENT OF COMPLIANCE

This trial will be conducted in accordance with the following:

- Protocol-related and trial-related documents
- Declaration of Helsinki
- Good Clinical Practice (GCP) as outlined by the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) E6 (R2) and regional regulations
- Regional subject data protection laws and regulations
- Other applicable regional and local regulations
- US Federal Regulations, as applicable

1. APPROVAL SIGNATURES

SPONSOR

I agree to conduct this trial in accordance with the requirements of this Clinical Trial Protocol and also in accordance with the following:

- Protocol-related and trial-related documents
- Declaration of Helsinki
- Good Clinical Practice (GCP) as outlined by the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) E6 (R2) and regional regulations
- Regional subject data protection laws and regulations
- Other applicable regional and local regulations
- Clinical trial contractual obligations
- US Federal Regulations, as applicable

CLINICAL TRIAL TITLE:

PaTHway TRIAL: A Phase 3, Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel Group Trial, with an Open-Label Extension, Investigating the Safety, Tolerability and Efficacy of TransCon PTH Administered Subcutaneously Daily in Adults with Hypoparathyroidism

See Appended Electronic Signature

PPD **, MD** Date

PPD

Ascendis Pharma, Inc.

2. SYNOPSIS

NAME OF SPONSOR/COMPANY	Ascendis Pharma Bone Diseases A/S
PRODUCT NUMBER/NAME	TransCon PTH (Palopegteriparatide)
PROTOCOL NUMBER	TCP-304
IND NUMBER	133469
EUDRACT NUMBER	2020-003380-26
DEVELOPMENT PHASE	3
PROTOCOL TITLE	**PaTHway TRIAL:** A Phase 3, Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel Group Trial, with an Open-Label Extension, Investigating the Safety, Tolerability and Efficacy of TransCon PTH Administered Subcutaneously Daily in Adult Subjects with Hypoparathyroidism
INDICATION	Hypoparathyroidism (HP) in Adults
OBJECTIVES	**Primary:** To assess the treatment effect of daily TransCon PTH on serum calcium (sCa) levels, and therapeutic doses of active vitamin D (i.e., calcitriol or alfacalcidol) and calcium at 26 weeks of treatment. **Secondary:** • To assess the safety and tolerability of daily TransCon PTH • To assess the treatment effect of daily TransCon PTH on hypoparathyroidism patient experience scale (HPES) domain scores • To assess the treatment effect of daily TransCon PTH on pharmacodynamic markers (including sCa) and active vitamin D and calcium doses • To assess the treatment effect of daily TransCon PTH on serum phosphate (sP), serum calcium x phosphate product (CxP) (albumin-adjusted sCa x sP product) and serum magnesium (sMg) • To assess anti-parathyroid hormone (PTH), anti-TransCon PTH and anti-polyethylene glycol (PEG) antibody responses • To assess the treatment effect during Extension Period • To assess the treatment effect of daily TransCon PTH on – Bone mineral density (BMD) and trabecular bone score (TBS) by Dual-energy X-ray absorptiometry (DXA) – Bone turnover markers (serum procollagen type 1 amino-terminal propeptide [P1NP] and c-telopeptide of type 1 collagen [CTx]) To assess the impact of treatment on patient-reported health related quality of life (QOL) and a clinician-reported outcome (ClinRO) assessment **Exploratory:** CCI [redacted]

PLANNED TRIAL SITES	Up to approximately 40 sites worldwide
PLANNED NUMBER OF SUBJECTS	Approximately 76
TRIAL POPULATION	Male and female adults with postsurgical chronic HP or autoimmune, genetic, or idiopathic HP, for at least 26 weeks; treated with either calcitriol ≥0.5 µg/day or alfacalcidol ≥1.0 µg/day and elemental calcium ≥800 mg/day for at least 12 weeks prior to Screening; and have a 24-hour urine calcium (uCa) excretion ≥125 mg/24h. **Note: The thresholds for calcitriol, alfacalcidol, and calcium are provided above in total daily doses. Acknowledging that the total daily doses may be taken in divided doses throughout the day, the corresponding thresholds would be calcitriol ≥0.25 µg twice daily [BID]; alfacalcidol ≥0.50 µg BID; calcium ≥400 mg BID**.
ELIGIBILITY CRITERIA	**Inclusion Criteria:** 1. Males and females, ≥18 years of age 2. Subjects with postsurgical chronic HP, or auto-immune, genetic, or idiopathic HP for at least 26 weeks. Diagnosis of HP is established based on historic hypocalcemia in the setting of inappropriately low serum PTH levels (Hypocalcemia is defined as a value below the reference range for normal at the performing laboratory. Inappropriately low serum PTH levels are defined as at or below the median value of the reference range for normal at the performing laboratory while the concomitant serum calcium is low. If specific lab results at the time of original diagnosis are not available, as historical diagnosis affirming these two components is adequate for inclusion) 3. Requirement for doses of standard of care (SoC) (e.g., calcitriol, alfacalcidol, calcium supplements) at or above a minimum threshold: • ***For countries other than Japan***: requirement for a dose of calcitriol ≥0.5 µg/day, or alfacalcidol ≥1.0 µg/day and (elemental) calcium ≥800 mg/day (e.g., calcium citrate, calcium carbonate etc.) for at least 12 weeks prior to Screening*. In addition, the dose of calcitriol, or alfacalcidol, or calcium should be stable** for at least 5 weeks prior to Screening • ***For Japan****:* requirement for a dose of calcitriol ≥1.0 µg/day, or alfacalcidol ≥2.0 µg/day for at least 12 weeks prior to Screening*. In addition, the dose of calcitriol or alfacalcidol should be stable** for at least 5 weeks prior to Screening. In Japan only (due to local practice and dietary patterns), there is no requirement to exceed a minimum dose of calcium supplements ** Excluding individuals receiving PTH-like drugs within 12 weeks of the screening visit, who need only demonstrate a stable requirement for elemental calcium and active vitamin D above minimum thresholds for 5 weeks prior to the screening visit.* *** Does not preclude occasional (≤2/week) PRN doses of calcium and/or active vitamin D for symptomatic hypocalcemia*

	4. Optimization of supplements prior to randomization to achieve the target serum levels of: • 25(OH) vitamin D levels of 20-80 ng/mL (49-200 nmol/L) **and** • Magnesium level in the normal range, or just below the normal range i.e.: ≥1.3 mg/dL (0.53 mmol/L) **and** • Albumin-adjusted or ionized sCa level in the normal range, or*just below the normal range, i.e.: – Albumin-adjusted sCa 7.8-10.6 mg/dL (or 1.95-2.64 mmol/L) – Ionized sCa 4.40-5.29 mg/dL (or 1.10-1.32 mmol/L) ** Just below the normal range implies the numerical range of 7.8-8.2 mg/dL (or 1.95-2.06 mmol/L) for albumin-adjusted sCa and the numerical range of 4.40-4.636 mg/dL (or 1.10-1.159 mmol/L) for ionized sCa* 5. The subject demonstrates a 24-hour uCa excretion of ≥125 mg/24h (on a sample collected within 52 weeks prior to Screening or during the Screening Period) **Note: Although 24-hour urine samples prior to Screening may be done on or off thiazide therapy, thiazide therapy is prohibited during the trial; and the 24-hour urine collection scheduled prior to Visit 1 must be done while off thiazides for at least 4 weeks prior to collection** 6. Body mass index (BMI) 17- 40 kg/m^2 at Screening 7. If ≤25 years of age, radiological evidence of epiphyseal closure based on X-ray of non-dominant wrist and hand 8. Thyroid-stimulating hormone (TSH) within normal laboratory limits within the 6 weeks prior to Visit 1; if on suppressive therapy for a history of thyroid cancer, TSH level must be ≥0.2 mIU/L 9. If treated with thyroid hormone replacement therapy, the dose must have been stable for at least 5 weeks prior to Screening 10. Estimated glomerular filtration rate (eGFR) ≥30 mL/min/1.73 m^2 during Screening 11. Able to perform daily subcutaneous (SC) self-injections of study drug (or have a designee to perform injections) via a pre-filled injection pen 12. Able and willing to provide written and signed Informed Consent Form (ICF) in accordance with Good Clinical Practice (GCP) 13. **For France only**: The subject is obligated to be affiliated with, or beneficiary of a social security system or assimilated. **Exclusion Criteria:** 1. Impaired responsiveness to PTH (pseudohypoparathyroidism) which is characterized as PTH-resistance, with elevated PTH levels in the setting of hypocalcemia 2. Any disease that might affect calcium metabolism or calcium-phosphate homeostasis or PTH levels other than HP, such as active hyperthyroidism; Paget disease of bone; severe hypomagnesemia; type 1 diabetes mellitus or poorly controlled type 2 diabetes mellitus (HbA1C >9%, documented HbA1C result drawn within 12 weeks prior to Screening is acceptable); severe and chronic liver, or renal

	disease; Cushing syndrome; multiple myeloma; active pancreatitis; malnutrition; rickets; recent prolonged immobility; active malignancy (other than low-risk well differentiated thyroid cancer or non-melanoma skin cancer); active hyperparathyroidism; parathyroid carcinoma within 5 years prior to Screening; acromegaly; or multiple endocrine neoplasia types 1 and 2 3. High risk thyroid cancer within 2 years, requiring suppression of TSH <0.2 mIU/L 4. Use of loop diuretics, phosphate binders (other than calcium supplements), digoxin, lithium, methotrexate, biotin >30 µg/day, or systemic corticosteroids (other than as replacement therapy) 5. Use of thiazide diuretic within 4 weeks prior to the 24-hour urine collection scheduled to occur within 1 week prior to Visit 1 6. Use of PTH-like drugs (whether commercially available or through participation in an investigational trial), including PTH(1-84), PTH(1-34), or other N-terminal fragments or analogs of PTH or PTH-related protein, within 4 weeks prior to Screening 7. Use of other drugs known to influence calcium and bone metabolism, such as calcitonin, fluoride tablets (>0.5 mg/day), strontium, or cinacalcet hydrochloride, within 12 weeks prior to Screening 8. Use of osteoporosis therapies known to influence calcium and bone metabolism, i.e., bisphosphonate (oral or intravenous [IV]), denosumab, raloxifene, or romosozumab therapies within 2 years prior to Screening 9. Non-hypocalcemic seizure disorder with a history of a seizure within 26 weeks prior to Screening **Note: History of seizures that occur in the setting of hypocalcemia is not exclusionary** 10. Increased risk for osteosarcoma, such as those with Paget's disease of bone or unexplained elevations of alkaline phosphatase, hereditary disorders predisposing to osteosarcoma, or with a prior history of substantial external beam or implant radiation therapy involving the skeleton 11. Pregnant or lactating women **Note: Acceptable highly effective contraception (**see Appendix 1**) is required for sexually active women of childbearing potential during the trial and for 2 weeks after the last dose of study drug, and pregnancy testing will be performed throughout the trial. Sexually active women of childbearing potential who are unwilling to use acceptable highly effective contraception are excluded from the trial** 12. Male who has a female partner who intends to become pregnant or is of childbearing potential and is unwilling to use adequate contraceptive methods during the trial **Note: Male subjects must use a condom, or his female partner of childbearing potential must use an effective form of contraception (as per CTFG definition), from the beginning of screening to the last trial visit**

	13. Diagnosed drug or alcohol dependence within 3 years prior to Screening 14. Disease processes that adversely affect gastrointestinal absorption, including but not limited to short bowel syndrome, significant small bowel resection, gastric bypass, tropical sprue, active celiac disease, active ulcerative colitis, active Crohn's disease, gastroparesis and autoimmune regulator (AIRE) gene mutations with malabsorption 15. Chronic or severe cardiac disease within 26 weeks prior to Screening including but not limited to congestive heart failure, myocardial infarction, severe or uncontrolled arrhythmias, bradycardia (resting heart rate <48 beats/minute, unless chronic and asymptomatic), symptomatic hypotension or systolic blood pressure (BP) <80 mm Hg or diastolic <40 mm Hg, or poorly controlled hypertension (systolic BP >165 mm Hg or diastolic >95 mm Hg). In the absence of a prior history of hypertension, an isolated BP >165/95 in the setting of white coat hypertension/anxiety may not be exclusionary and a measurement can be repeated prior to randomization 16. Cerebrovascular accident within 5 years prior to Screening 17. Within 26 weeks prior to Screening: acute colic due to nephrolithiasis, or acute gout. Subjects with asymptomatic renal stones are permitted 18. Participation in any other interventional trial in which receipt of investigational drug or device occurred within 8 weeks or within 5.5 times the half-life of the investigational drug (whichever comes first) prior to Screening 19. Any disease or condition that, in the opinion of the investigator, may require treatment or make the subject unlikely to fully complete the trial, or any condition that presents undue risk from the investigational product or procedures, including treated malignancies that are likely to recur within the approximate 3.5-year duration of the trial 20. Known allergy or sensitivity to PTH or any of the excipients [metacresol, mannitol, succinic acid, NaOH/(HCl)] 21. Likely to be non-compliant with respect to trial conduct 22. Any other reason that in the opinion of the investigator would prevent the subject from completing participation or following the trial schedule
TRIAL DESIGN	This is a Phase 3, multicenter, randomized, double-blind, placebo-controlled, parallel group, 26-week trial, with an open-label extension of 3 years of daily TransCon PTH in male and female adults with either postsurgical chronic HP or autoimmune, genetic, or idiopathic HP for at least 26 weeks, treated with calcitriol (an active vitamin D) ≥0.5 µg/day, or alfacalcidol (an active vitamin D) ≥1.0 µg/day and elemental calcium ≥800 mg/day for at least 12 weeks prior to Screening.

	Screening Period (Week -6 to Week -2): The Screening Period consists of determining eligibility (including determining on a historical test within 52 weeks prior to Screening or a test during Screening that 24-hour uCa excretion is ≥125 mg/24 hr), and optimizing vitamin D, calcium and magnesium levels, and doses of SoC (active vitamin D and calcium) prior to study drug (TransCon PTH or placebo) dosing to achieve the following target serum levels: • 25(OH) vitamin D: 20-80 ng/mL (49-200 nmol/L) • Magnesium: within the normal range, or just below the normal range i.e.: ≥1.3 mg/dL (0.53 mmol/L) • Albumin-adjusted or ionized sCa: within the normal range, or just below the normal range, i.e.: – Albumin-adjusted sCa 7.8-10.6 mg/dL (or 1.95-2.64 mmol/L) – Ionized sCa 4.40-5.29 mg/dL (or 1.10-1.32 mmol/L) Therapeutic doses of calcitriol, alfacalcidol, calcium, magnesium and Vitamin D3 are adjusted only after initial Screening laboratory results are received. Follow-up laboratory assessments of the above values, with the exception of 25(OH) vitamin D levels, are performed approximately 3 days after every dose adjustment during the Screening Period; the 25(OH) vitamin D level may be rechecked ≥7 days from any dose change. If required, additional dose adjustments, with follow-up laboratory assessments approximately 3 days later may be performed throughout the Screening Period. For additional guidance see Section 9.5.1. When laboratory results are within the above optimization ranges and all other entry criteria are met, the subject is eligible to move to the Blinded Treatment Period and be randomized following confirmation by the Medical Monitor or designee. Following randomization, it is recommended to start the treatment period (Visit 1) within 2 weeks from the time of randomization. The Screening Period may be extended with Medical Monitor approval for subjects who fail to achieve values within the target laboratory ranges within the Screening window. **Blinded Treatment Period (Visit 1 - 10; Week 0-26):** Subjects will be randomized 3:1 to receive either TransCon PTH or placebo: • TransCon PTH 18 µg/day*, co-administered with SoC • Placebo for TransCon PTH (excipient solution) 18 µg/day, co-administered with SoC * *Dose of TransCon PTH refers to dose of PTH(1-34) administered* Randomization will be stratified by etiology of hypoparathyroidism (post-surgical vs other). All subjects will start with study drug 18 µg/day and will be individually and progressively titrated to an optimal dose in dose increments of 3 µg/day. **Blinded Treatment Period Visit 1-10 (Weeks 0-26):** **Visit 1:** Start study drug 18 µg/day **and** decrease active vitamin D dose by 33-50% (e.g., skip 2nd dose of the day if taking BID, skip final dose of the day if taking three times daily (TID), or reduce once daily dose of alfacalcidol ≥1.0 µg by 50% (≥0.5 µg).

	Subsequently, subjects will attend frequent clinic visits and laboratory visits (LV) (LV1, LV2, LV3) to measure sCa levels. Assuming albumin-adjusted or ionized sCa remains ≥ the lower limit of normal (LLN) and ≤ the upper limit of normal (ULN), **SoC doses** will be progressively withdrawn. Complete guidance on SoC titration during the Blinded Treatment Period is provided in Section 9.5.2.1 and Appendix 2. Because this trial is assessing the potential for TransCon PTH to be a parathyroid hormone replacement therapy, a goal is for subjects to achieve independence from standing doses of calcitriol, alfacalcidol, and calcium supplements. **Note: In case needed to meet recommended dietary intake of calcium, it is permitted to take calcium supplements ≤600 mg/day as a nutritional supplement for the sake of reaching the recommended dietary intake. The calcium dose of ≤600 mg/day is considered as "supplemental" to meeting recommended daily intake for general health, as opposed to a "therapeutic" dose to treat hypoparathyroidism. The progressive cessation of calcitriol, alfacalcidol, and calcium should occur while increasing the dose of TransCon PTH to achieve normocalcemia.** Meanwhile, **study drug doses** can be increased by 3 µg/day as long as ≥7 days have elapsed since a prior dose adjustment in study drug. Gradual increases in study drug doses may facilitate gradual reduction and eventual cessation of SoC. Alternatively, study drug doses can be decreased by 3 µg/day for serum calcium levels that continue to be high even after all SoC has been withdrawn. The study drug dose range for this trial is 6-60 µg/day, and will be supported by 3 pen presentations delivering discrete doses of 6, 9, and 12 µg/day; 15, 18, and 21 µg/day; and 24, 27, and 30 µg/day, respectively. Complete guidance on study drug titration during the Blinded Treatment Period is provided in Section 9.5.2.2 and Appendix 2. Per the Schedule of Events, initial clinic visits and LVs occur relatively frequently to accommodate dose titration of study drug, and occur less frequently later on (see Appendix 3 and Appendix 4). **Open-Label Extension Period (Visits 10+; Weeks 26+):** At Visit 10 (Week 26), all subjects will be assigned to open-label treatment as follows: • **If still taking active vitamin D:** Start TransCon PTH at a dose of 18 µg/day, and subsequently follow the titration algorithm as per Appendix 2 • **If NOT taking active vitamin D:** – **And taking study drug ≥ 30 µg/day:** Start TransCon PTH at a dose of 18 µg/day, and subsequently follow the titration algorithm per Appendix 2 – **And taking study drug dose < 30 µg/day:** Start TransCon PTH at the same dose of study drug taken at the end of the Blinded Treatment Period. Exception: In cases of an out-of-range sCa level at Visit 10, adjust the TransCon PTH and/or calcium doses as per Appendix 2

	TransCon PTH doses can be increased by 3 µg/day as long as ≥7 days have elapsed - since a prior dose adjustment in study drug. Gradual increases in study drug doses may facilitate gradual reduction and eventual cessation of SoC. Alternatively, study drug doses can be decreased by 3 µg/day for sCa levels that continue to be high even after all SoC has been withdrawn. **Note: At all times during the trial, subjects with symptoms of hypocalcemia may take PRN doses of calcium (preferred) and/or active vitamin D, and/or do an Unscheduled Laboratory Visit (ULV) to measure sCa levels. Based on the sCa level, the investigator may titrate the SoC and/or study drug dose per** Appendix 2**. Due to the long half-life of TransCon PTH, the full effect of a dose level occurs by approximately 7 days after a dose change.**
INVESTIGATIONAL PRODUCT	Name: TransCon PTH TransCon PTH drug product is supplied as a solution with a concentration of 0.3 mg PTH(1-34)/mL in a single-patient-use prefilled pen intended for SC injection. Excipients include metacresol, mannitol, succinic acid, and NaOH/(HCl). The TransCon PTH delivery system consists of a multi-use cartridge integrated into a device to constitute a prefilled injection pen. The cartridge contains compounded solution of TransCon PTH or placebo TransCon PTH. Three presentations of the prefilled pen containing TransCon PTH drug product for 14 days usage at room temperature below 86°F (30°C) are available. The three pen presentations are 6, 9, and 12 µg/day; 15, 18, and 21 µg/day; and 24, 27 and 30 µg/day, respectively. The TransCon PTH drug product concentration is 0.3 mg PTH(1-34)/mL, so the delivered volume across the dose range of 6 to 30 µg/day is 20 to 100 µL.
REFERENCE PRODUCT(S)	Placebo for TransCon PTH drug product (excipient solution in the pens) in three pen presentations to mimic dose ranges of 6, 9, and 12 µg/day; 15, 18, and 21 µg/day; and 24, 27 and 30 µg/day within the Blinded Treatment Period.
TREATMENT REGIMEN	Daily treatment with TransCon PTH or placebo for TransCon PTH (excipient solution) delivered by a modified Ypsomed UnoPen Fix pen injector using 31G x5 mm pen needles to deliver doses of 6-30 µg/day in a volume of ≤100 µL, to either abdomen or anterior thigh, rotating injection sites. The TransCon PTH allowed dose range will be 6-60 µg/day. All doses >30 µg/day will be delivered in the form of two single doses injected one after another at different injection sites using two pens. All treatment groups may continue to take doses of magnesium and vitamin D3 to maintain the defined ranges.
BLINDING	This trial consists of a 26-week randomized, double-blind, placebo-controlled treatment period followed by an open-label Extension Period of up to 156 weeks. To maintain the double-blind during the Blinded Treatment Period, the subjects will be randomized 3:1 to either receive initially 18 µg/day of TransCon PTH or placebo for TransCon PTH (excipient solution).

TRIAL AND TREATMENT DURATION	The total duration of the trial for an individual subject is expected to be up to approximately 190 weeks including up to approximately 4 weeks of Screening, a 182-week treatment period and a 2 weeks of follow up period after last study drug administration (plus a recommended period of up to approximately 2 weeks between randomization and Visit 1). • **Blinded Treatment Period:** 26 weeks • **Extension Period (open-label TransCon PTH treatment):** 156 weeks Only subjects who successfully complete the Blinded Treatment Period on blinded study drug may enter the open-label Extension Period (TransCon PTH only).
STOPPING RULES	Study drug may be temporarily held for symptomatic hypercalcemia. The study drug may be discontinued for severe intractable hypo- or hypercalcemia for 2 weeks that cannot be corrected with dose adjustments of SoC and/or TransCon PTH. Reinstitution of the study drug, in such cases requires prior approval by the Medical Monitor. In case the study drug is permanently discontinued prior to Visit 10, subjects are expected to continue in the trial without taking study drug until Visit 10. If the study drug is permanently discontinued after Visit 10, subjects are withdrawn from the study following an Early Termination Visit.
ENDPOINTS	**Primary Efficacy Endpoint:** At 26 weeks of treatment, the proportion of subjects with: • Albumin-adjusted sCa measured within 4 weeks prior to and on the Week 26 visit are within the normal range (8.3-10.6mg/dL) *; **and** • Independence from active vitamin D** **and** • Independence from therapeutic doses of calcium (i.e., taking calcium supplements ≤600 mg/day). This dose of calcium ≤600 mg/day in the form of tablets, powder, liquid suspension, or transdermal patch is considered as "supplemental" to meeting recommended daily intake for general health, as opposed to a "therapeutic" dose to treat hypoparathyroidism*** **and** • No increase in prescribed study drug within 4 weeks prior to Week 26 visit**** * Except for at the Week 26 visit, confirmation that an albumin-adjusted sCa is "abnormal" requires 2 consecutive results outside the normal range within 4 weeks prior to the Week 26 visit. **Independence from active vitamin D will be defined as a daily standing dose equal to zero on all days AND use of any PRN vitamin D ≤7 days within 4 weeks prior to the Week 26 visit. ***Independence from therapeutic calcium will be defined as average daily standing dose ≤600 mg AND use of PRN doses on ≤7 days within 4 weeks prior to the Week 26 visit. • ****Dose decrease permitted for safety reasons. **Key Secondary Efficacy Endpoints:** Change from baseline at 26 weeks of treatment: • HPES symptom – Physical domain score • HPES Symptom – Cognitive domain score

	• HPES Impact - Physical functioning domain score • HPES Impact – Daily life domain score • 36-Item Short Form Survey (SF-36) Physical functioning subscale score **Other Secondary Efficacy Endpoints:** The key secondary efficacy endpoints and the following efficacy endpoint will be evaluated at predefined timepoints during the Extension Period. • The proportion of subjects that meet the following criteria: – Albumin-adjusted sCa measured within the normal range (8.3-10.6 mg/dL); and – Independence from active vitamin D (i.e., standing dose of active vitamin D equal to zero on the day prior to the Week 52 visit or other visits of interest); and – Independence from therapeutic doses of calcium (i.e., standing dose of elemental calcium ≤ 600 mg on the day prior to the Week 52 visit or other visits of interest). The following endpoints will be evaluated at predefined timepoints during the Blinded Treatment and the Extension Period: • Calcium and active vitamin D doses • Daily "pill burden" of active vitamin D and calcium (as oral tablets, powder, liquid solutions, liquid suspensions, or transdermal patches) • sP • Albumin-adjusted sCa x sP product, including proportion of subjects with albumin-adjusted sCa x sP product ≤55 mg^2/dL^2, ≤52 mg^2/dL^2, and ≤44 mg^2/dL^2 • Albumin-adjusted sCa • BMD and TBS by DXA • Bone turnover markers (serum P1NP and CTx) • sMg • EuroQol 5-Dimensional Questionnaire (EQ-5D) • Clinical Global Impression of Severity (CGI-S) • HPES: HPES Impact domain scores (Psychological Well-being and Social life and Relationships) and HPES Symptom and Impact total scores • SF:36: SF-36 subscale scores (Role Limitations due to Physical Health Problems, Bodily Pain, General Health, Vitality, Social Functioning, Role Limitations due to Emotional Problems, and Mental Health) and SF-36 component scores (Physical component score and Mental component score) **Safety Endpoints:** The following safety endpoints will be assessed during the Blinded Treatment and Extension Periods: • Incidence of adverse events (AEs), adverse events of special interest (AESI) and serious adverse events (SAEs) • Serum chemistry, hematology

	• 24-hour urine chemistry (including urine calcium and urine creatinine clearance) at prespecified timepoints including at Week 26 • Clinical events of hypo- or hypercalcemia (emergency/urgent care visits and hospitalizations) • Injection site tolerability (based on AEs) • Evaluation of anti-PTH, anti-TransCon PTH and anti-PEG antibody responses • Vital signs **Exploratory Endpoints:** CCI [redacted]
END OF TRIAL	The end of trial (EOT) is defined as the last subject last visit.
STATISTICAL METHODS	Details of applicable statistical methods will be provided in a Statistical Analysis Plan (SAP) which will be finalized before trial unblinding and database lock of the Blinded Treatment Period. If discrepancies exist between the text of the statistical analysis as planned in the protocol and the final SAP, the final SAP will define the planned analysis of record. The Intent-To-Treat (ITT) Population consists of all subjects who were randomized and received at least one dose of blinded study drug. All efficacy analysis will be based on ITT and treatment assignment per randomization. The Safety Analysis Population consists of all randomized subjects who received at least one dose of study drug. The safety analyses will be based on the Safety Analysis Population and actual treatment received. In general, data from clinical assessments will be summarized using descriptive statistics. Categorical data will be presented using counts and percentages of subjects. Continuous variables will be presented using number of subjects, mean, standard deviation (SD)/standard error (SE), median, minimum and maximum. All statistical tests will be two-sided and tested at the statistically significant level of 0.05. Confidence intervals will be 2-sided 95% confidence intervals, unless stated otherwise. The primary analysis will use the CMH (Cochran-Mantel-Haenszel) test stratified by etiology of hypoparathyroidism (post-surgical vs other) to compare the proportion of subjects meeting the listed criteria of the primary endpoint (responders vs. non-responders) in the TransCon PTH vs. placebo groups. Sequential testing will be applied to control the multiplicity for the primary and key secondary endpoints. Details will be specified in the SAP. All efficacy endpoints will be summarized descriptively in Extension Period analysis.

SAMPLE SIZE DETERMINATION	The sample size is determined based on considerations from both statistical power and adequate safety exposure perspectives. Assuming that the response rate is 70% for TransCon PTH and 15% for placebo for the primary endpoint at 26 weeks, 68 subjects randomized 3:1 to active TransCon PTH vs. placebo will have approximate statistical powers of 99% at alpha = 0.05, and 95% at alpha = 0.01 (two-sided) to demonstrate statistically significant difference between TransCon PTH and placebo. Taking into account of approximately 10% dropout, a total sample size of 76 is targeted.

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4. LIST OF ABBREVIATIONS AND DEFINITIONS

Abbreviation	Definition
AC	arterial calcification
AE	adverse events
AESI	adverse events of special interest
AIRE	autoimmune regulator
BID	twice daily
BMD	bone mineral density
BMI	body mass index
BP	blood pressure
CFR	Code of Federal Regulations
CGI-S	clinical global impression of severity
ClinRO	clinician-reported outcome
Cmax	maximum concentration
CMH	Cochran-Mantel-Haenszel
COA	clinical outcome assessment
CRO	contract research organization
CTFG	Clinical Trial Facilitation Group
CTx	c-telopeptide of type 1 collagen
CxP	calcium-phosphate product
DMC	Data Monitoring Committee
DXA	dual-energy X-ray absorptiometry
ECG	electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture
eGFR	estimated glomerular filtration rate
EOT	end of trial
EQ-5D	euroQol 5-dimensional
EQ-5D-5L	euroQol 5-dimensional five-level
EQ-VAS	euroQol visual analogue scale
EC	ethics committee
FDA	Food and Drug Administration
FECa	fractional excretion of calcium
FSH	follicle stimulating hormone
GCP	good clinical practice

Abbreviation	Definition
hCG	human chorionic gonadotropin
HP	hypoparathyroidism
HPES	hypoparathyroidism patient experience scale
ICF	informed consent form
ICH	International Council for Harmonisation Technical Requirements for Pharmaceuticals for Human Use
IFU	instructions for use
IM	investigator meeting
IRB	institutional review board
IRT	interactive response technology
ITT	Intent-To-Treat
ISR	injection site reaction
IUD	intrauterine device
IUS	intrauterine hormone-releasing system
IV	intravenous
LAM	lactational amenorrhoea method
LLN	lower level of normal
LV	Laboratory Visit
MAD	multiple ascending dose
MedDRA	medical dictionary for regulatory activities
mPEG	methoxypolyethylene glycol
MTD	maximum tolerated dose
NIH	National Institutes of Health
NOAEL	no-observed-adverse-effect level
P1NP	procollagen type 1 amino-terminal propeptide
CCI	[redacted]
PD	pharmacodynamics
PEG	polyethylene glycol
PI	principal investigator
PK	pharmacokinetics
pQCT	peripheral quantitative computed tomography
PTH	parathyroid hormone
PRN	As needed. Used interchangeably with “rescue”
PRO	patient-reported outcome

Abbreviation	Definition
QOL	quality of life
RDA	recommended daily allowance
SAD	single ascending dose
SAE	serious adverse events
SD	standard deviation
SE	standard error
SAP	statistical analysis plan
SC	subcutaneous
sCa	serum calcium
SF-36	36-item short form survey
SIV	site initiation visit
sMg	serum magnesium
SoC	standard of care (active vitamin D plus calcium)
SOP	standard operating procedure
sP	serum phosphate
SUSAR	suspected unexpected serious adverse reaction
TBS	trabecular bone score
TEAE	treatment-emergent adverse event
TID	three times daily
TPTx	thyroparathyroidectomized
TSH	thyroid-stimulating hormone
uCa	urine calcium
uP	urine phosphate
ULN	upper level of normal
ULV	unscheduled laboratory visit
UV	unscheduled visit
CCI	[redacted]

Definition Used	Explanation
Study Drug	Refers to TransCon PTH or Placebo
Active vitamin D	Refers to therapeutic calcitriol (1,25-dihydroxyvitamin D3) or alfacalcidol (1α-hydroxyvitamin D3, an analogue of active vitamin D)
Standard of Care (SoC)	Is equivalent to conventional therapy, i.e., active vitamin D and calcium supplements

5. INTRODUCTION

5.1. BACKGROUND AND RATIONALE

5.1.1. Parathyroid Hormone

Parathyroid hormone (PTH) is a product of endocrine secretion from the four parathyroid glands. It is synthesized by chief cells as a prohormone peptide, eventually cleaved to 84 amino acids, i.e., PTH(1-84), which is secreted. Although PTH(1-84) is the biologically active form of PTH, receptor-mediated activities require only the 34 amino acid N-terminus fragment, PTH(1-34). PTH(1-84) is fairly quickly cleaved to PTH(1-34) both by the parathyroid glands and by hepatic Kuppfer cells (Hamilton 1983). PTH(1-33) appears to equipotent to PTH(1-34) (Morley 1999).

PTH maintains the body's extracellular calcium and phosphate homeostasis, the former within a very narrow range. When serum calcium (sCa) levels drop, PTH is released from the parathyroid glands. An important effect of PTH at the renal PTH/PTHrP receptor is to increase calcium reabsorption, decrease phosphate reabsorption, and convert the prohormone 25-hydroxyvitamin D (25OHD) to the fully active steroid hormone, 1,25-dihydroxyvitamin D [1,25D$(OH)_2$ vitamin D3 or calcitriol]. Active vitamin D increases calcium and phosphate absorption in the small intestine. Another direct action of PTH is to increase osteoclast activity causing calcium and phosphate to increase and potentially osteocyte activity, increasing ionized calcium.

5.1.2. Hypoparathyroidism

Hypoparathyroidism (HP) is a rare disease of impaired PTH production or activity. The majority of cases (≥75%) are acquired, occurring secondary to anterior neck surgery in which approximately 0.12-4.6% of procedures cause the parathyroid gland(s) to be inadvertently injured or destroyed (Brandi 2016, Clarke 2016). Of these, 3-30% result in chronic HP, i.e., features of HP lasting more than 6 months after the surgery (Mannstadt 2013, Brandi 2016, Shoback 2016). Autoimmune diseases are the second most common cause of acquired HP while less common causes include intrinsic genetic defects of the parathyroid glands, hemochromatosis, magnesium deficiency, as well as idiopathic disease (Brandi 2016, Clarke 2016).

The US prevalence rate of HP is estimated to range from 60,000-115,000, thus meeting orphan disease status (Brandi 2016). Given the predominance of cases secondary to anterior neck surgery, HP incidence rates depend on the number of anterior neck surgeries performed in a given locale, the expertise of the surgeons, and underlying pathology.

In HP, the sCa level drops and there is a lack of compensatory PTH secretion, so calcium-phosphate homeostasis is disrupted. The kidneys decrease calcium reabsorption, phosphate excretion, and conversion of 25OHD to active 1,25$(OH)_2$D. Given decreased 1,25$(OH)_2$D conversion in the kidneys, intestinal absorption of calcium and phosphate decline and due to deficient PTH the bone osteoclast activity is decreased, further decreasing sCa and resulting in over-mineralized bone and higher-than-normal bone mineral density (BMD). Despite decreased gastrointestinal absorption of phosphate from decreased 1,25$(OH)_2$D production, patients with HP typically show either elevated or high-normal levels of serum phosphate (sP) due to decreased renal phosphate excretion.

5.1.3. Current Standard Therapy for Hypoparathyroidism

Current Standard of Care (SoC) for HP – specifically active vitamin D and high doses of calcium – may improve hypocalcemia, particularly in patients with mild/moderate HP; active vitamin D stimulates calcium and phosphate absorption from the intestines and calcium supplements increase sCa (Brandi 2016). Yet, chronic calcium and vitamin D therapy may also produce adverse effects beyond the original problems of HP because active vitamin D and calcium do not restore PTH-dependent renal calcium reabsorption, correct the elevated sP in HP, or correct diminished bone turnover (Winer 2012, Mannstadt 2017). Patients on SoC may become hypercalciuric, with a subsequent risk for nephrolithiasis, nephrocalcinosis, and chronic kidney disease (Winer 2012, Mannstadt 2017). Decreased PTH activity also leads to decreased bone resorption, i.e., a low bone turnover – high bone mass state. Finally, as SoC increases both sCa (which is low in HP) and sP (which is elevated in HP), SoC can also result in an increased calcium-phosphate product (CxP), thereby increasing the risk for ectopic calcifications, including in the vascular system, the renal parenchyma, the lens of the eye, and the basal ganglia of the central nervous system (Abate 2017).

Based on the current SoC, there have been six goals of chronic HP therapy: 1) prevent signs and symptoms of hypocalcemia; 2) maintain sCa concentration slightly below or within the low-normal range; 3) maintain the CxP below 55 mg^2/dL^2 (4.4 $mmol^2/L^2$); 4) avoid hypercalciuria; 5) avoid hypercalcemia; and 6) avoid renal (nephrocalcinosis/nephrolithiasis) and other extra-skeletal calcifications (Bilezikian 2016, Brandi 2016).

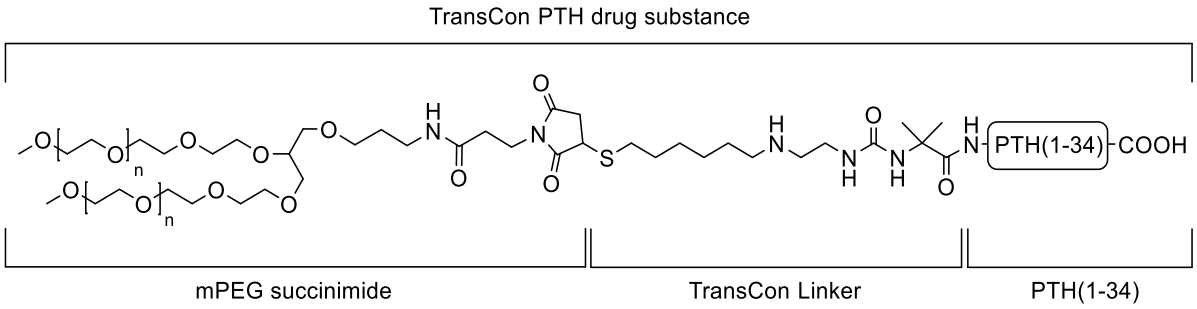
In the absence of a true PTH replacement therapy that replaces active PTH within the normal physiologic range 24 hours per day, achieving all six goals of HP therapy is a challenge. Furthermore, given that active vitamin D and calcium may cause paradoxical long-term morbidity and mortality, replacing the missing hormone in HP patients has long been desired. In 1996, Winer et al established the experimental basis for using biologically active PTH(1-34) to treat HP (Winer 1996). Since then, twice daily (BID) administration has been shown to achieve better calcemic control than daily, and continuous infusion has been shown to achieve better control than BID (Winer 1998, Winer 2008, Winer 2012). In addition to normalizing both sCa, sP, and serum magnesium (sMg), PTH by continuous infusion has also demonstrated less sCa fluctuations, a reduction in urine calcium (uCa), and normalized bone turnover compared to BID PTH(1-34) administration, despite a 65% lower dose of infused vs BID PTH(1-34) (Winer 2012). While intermittent PTH administration results in high hormone fluctuations, with an initial supraphysiological PTH level [high maximum concentration (C_{max})] followed by a rapid decline to subtherapeutic levels, continuous infusion maintains PTH levels in the physiological range throughout the day. Although PTH(1-34) is currently only approved for osteoporosis, these studies provided proof of concept for its use in HP. Thus, with a treatment that provides active PTH within the lower half of the normal range for 24 hours per day, it should be possible to change the 2nd goal to maintaining a sCa concentration within the normal range, while achieving the remaining 5 goals.

Recombinant PTH(1-84) (Natpara, trademark owned by Takeda) was approved as an adjunct to active vitamin D and calcium by the Food and Drug Administration (FDA) in 2015 (BLA #125511 2015) using PTH to treat HP. In its Advisory Meeting Briefing Document, the FDA noted that “This [lack of control of urinary calcium excretion] is primarily due to the short half-life (~ 3 hours) of Natpara, which results in PTH concentrations returning to baseline by

10-12 hours", and also noted that Natpara did not reduce the clinical episodes of either hypocalcemia or hypercalcemia compared to placebo plus SoC (Briefing Document 2014, Khurana 2019). Using a calcium homeostasis systems pharmacology model, the FDA simulated effects following 100 µg daily or BID dosing of 50 µg and compared these regimens against a theoretical slow-release model. It concluded that PTH replacement therapy requires a physiologic profile, specifically a dosing regimen that is either more frequent than daily dosing or daily dosing with a slow-release formulation that achieves an infusion-like exposure within the physiological normal range; both of which the model predicted would decrease renal calcium excretion (Khurana 2019). In April 2017, once-daily subcutaneous (SC) injection administration of recombinant PTH(1-84) (Natpar) was approved in Europe as a new therapy and recommended for adult patients with HP who cannot be well controlled on conventional therapy alone (CHMP 2017). However, CHMP noted that this treatment has not demonstrated the ability to reduce the incidence of hypocalcemia, hypercalcemia, or hypercalciuria relative to the conventional therapy of oral calcium and active vitamin D analogues, due to its relatively short half-life of ~3 hours (CHMP 2017). On 9/5/2019, FDA removed Natpara from the US market due to safety concerns about rubber particles from the vial septum; it remains not commercially available in the US.

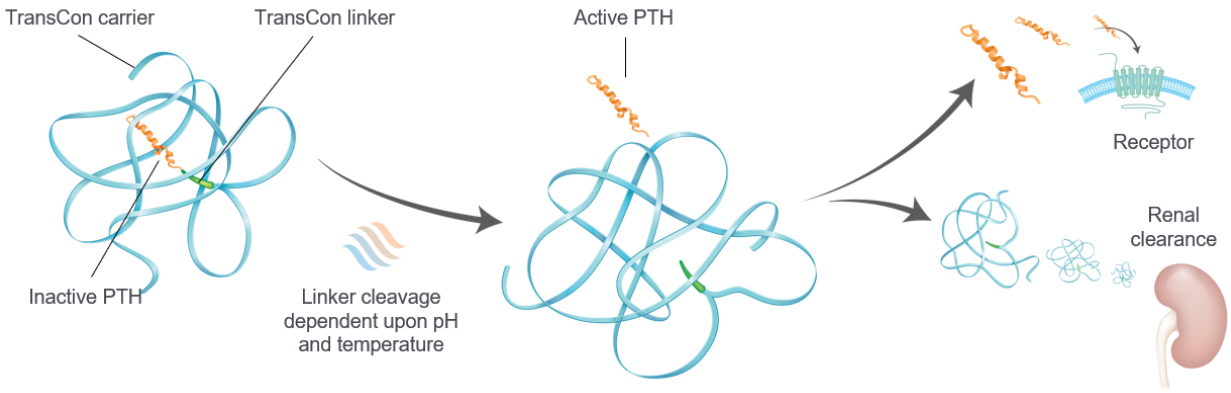
TransCon PTH is a prodrug consisting of PTH(1-34) transiently conjugated to a branched 40 kDa methoxypolyethylene glycol (mPEG) moiety through a proprietary TransCon Linker as illustrated in Figure 1.

Figure 1: Structure of TransCon PTH



TransCon PTH is administered as a once-daily SC and is designed to maintain a steady concentration of PTH in the blood stream within the normal physiological range for 24 hours per day. After SC injection, auto-cleavage of TransCon PTH occurs in a controlled manner by first-order kinetics, whereby active PTH is released as either PTH(1-34) or PTH(1-33) (major metabolite) from the TransCon Linker at a rate proportional to the prodrug concentration. The carrier inactivates PTH and shields it from clearance and receptor binding and uptake. Following release from the prodrug, active PTH retains the original mode of action (i.e., binding to the PTH receptor 1) and the TransCon Linker-mPEG is cleared primarily by renal excretion (see Figure 2).

Figure 2: Illustration of the TransCon PTH Technology and the Release of Active PTH



5.2. RELEVANT FINDINGS FROM NONCLINICAL STUDIES

Please refer to the current version of the TransCon PTH Investigator's Brochure *Section 4 – Nonclinical Studies* for a full summary of the nonclinical data.

A comprehensive nonclinical development program has been conducted for TransCon PTH to support clinical development. The testing strategy involved a range of in silico, in vitro and in vivo studies in Sprague Dawley rats, cynomolgus monkeys, and New Zealand White rabbits to characterize the pharmacokinetics (PK), TK, PD, and safety profile of TransCon PTH. Bioanalytical assays, including immunogenicity assays were developed and validated according to relevant guidelines.

In vivo safety assessment was based on standard toxicological endpoints and assessment of bone turnover markers, peripheral quantitative computed tomography (pQCT), dual-energy X-ray absorptiometry (DXA), and histomorphometry.

The pharmacological effect of TransCon PTH was demonstrated in single-dose PK/PD and in repeat-dose toxicity studies in rats, monkeys, and rabbits. The pharmacological effect was further confirmed in thyroparathyroidectomized (TPTx) rats, a disease model for HP.

In repeat-dose toxicity studies the no-observed-adverse-effect level (NOAEL) for SC daily administrations of TransCon PTH for up to 26 weeks was 10 µg PTH(1-34)/kg in rats and 0.5 µg PTH(1-34)/kg in monkeys. The adverse findings considered related to TransCon PTH were all considered exaggerated pharmacological effects of continuous administration of PTH resulting in sustained hypercalcemia. TransCon PTH did not induce any adverse effects on the central nervous, pulmonary, or cardiovascular system, and was not considered genotoxic as assessed in specific genotoxicity studies. Furthermore, the reproductive and developmental toxicity studies conducted so far have not identified any adverse effects on embryofetal development or fertility.

5.3. CLINICAL EXPERIENCE

A Phase 1 clinical trial [a randomized, placebo-controlled, single ascending dose (SAD) and multiple ascending dose (MAD) trial to evaluate the safety, tolerability, pharmacodynamics (PD), and PK of TransCon PTH in healthy adult subjects] conducted under good clinical practice (GCP), ethics committee (EC), and Declaration of Helsinki guidelines has been completed.

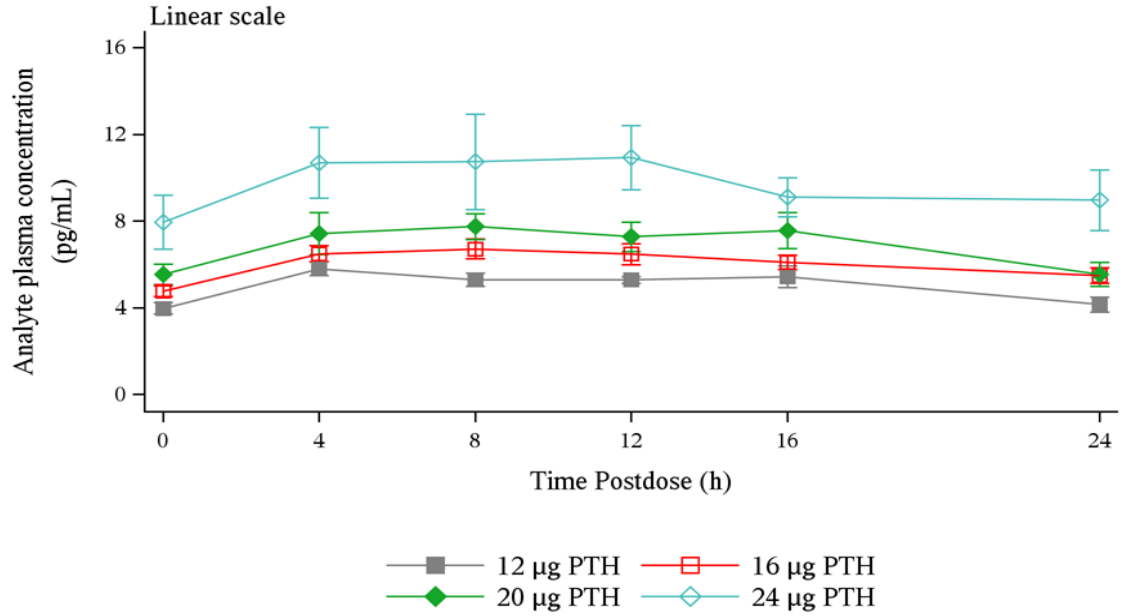
A total of 132 male and female normal healthy subjects were randomized and received study treatment; 69 subjects in 7 SAD cohorts [56 received TransCon PTH and 13 placebo (3.5, 12, 32, 48, 72, 100, and 124 µg/day PTH)] with a maximum tolerated dose (MTD) of 124 µg PTH and 63 subjects in 6 MAD cohorts [50 received TransCon PTH and 13 placebo (3.5, 7.0, 12, 16, 20, and 24 µg/day PTH)] with a MTD of 20 µg PTH/day.

The primary goal of the trial was to identify the clinically effective dose range for the Phase 2 clinical trial (based on change in albumin-adjusted sCa from baseline), the effect of treatment on the fractional excretion of calcium (FECa), and to assess the PK profile, safety, tolerability, and immunogenicity of TransCon PTH.

In healthy volunteers in SAD cohorts, TransCon PTH demonstrated dose-dependent increases in Free PTH, corresponding to the sum of active Free PTH [intact Free PTH(1-34)] and the main metabolite Free PTH(1-33) in the calculated normal range, which correlated with dose-dependent increases in albumin-adjusted sCa and suppression of intact PTH(1-84) at all single doses of ≥32 µg. Despite mild hypercalcemia over 3 days in the cohorts receiving single doses of TransCon ≥100 µg PTH, at the time of greatest sCa (mean ±SD of 10.3±0.23 to 10.97±0.56 mg/dL on Day 2), the urine FECa remained well-controlled below the upper level of normal (ULN) of the normal range (2%), demonstrating that active PTH within the normal range continuously over 24 hours can enhance the renal handling of calcium.

Figure 3 shows a dose-dependent increase in Free PTH, with a low peak-to-trough ratio of ~1.27 to 1.55 over 24 hours. Phase 1 data demonstrate that the effective half-life of Free PTH released from the prodrug is ~60 hours, with Free PTH approaching steady-state by Day 8 after dosing. This is further supported by sparse PK sampling performed in the Phase 2 trial (TransCon PTH TCP-201). The normal physiologic range for intact PTH(1-84) is 10-65 pg/mL; as PTH(1-34) and PTH(1-33) comprise about 40% of the molecular mass of the intact hormone, the calculated normal range is about 4-26 pg/mL.

Figure 3: Arithmetic Mean Plasma Concentrations of Free PTH on Day 10

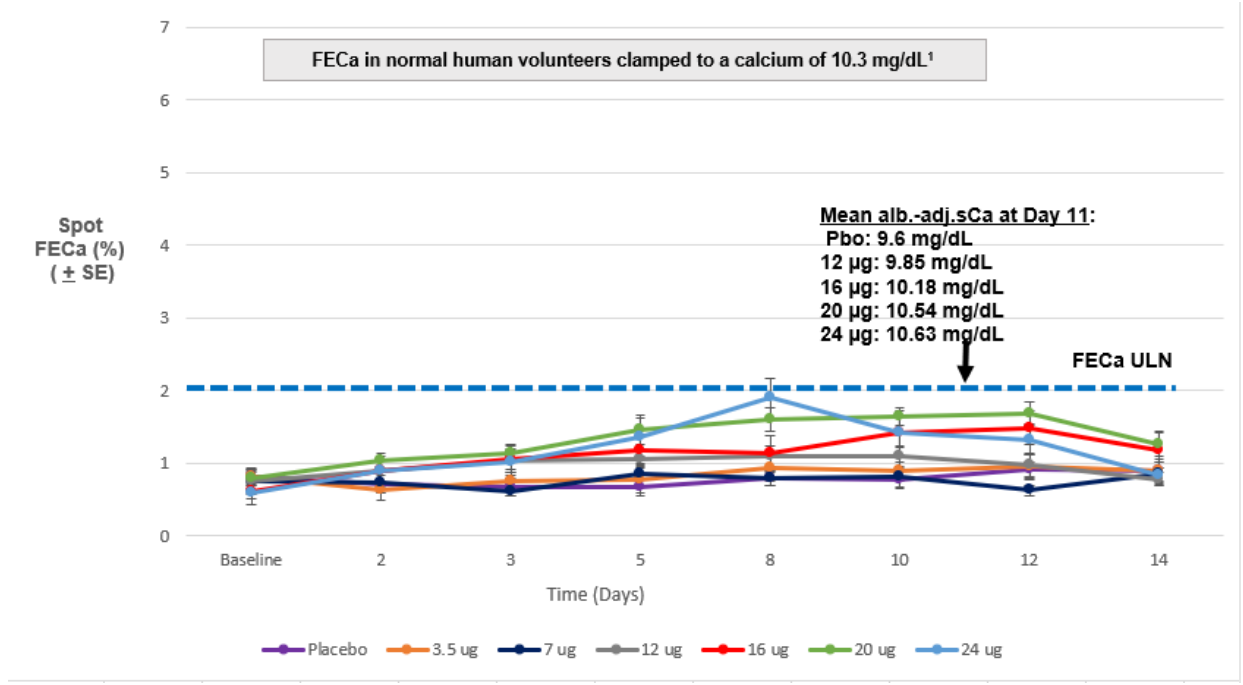


Note: Negative SE bars less than 0 are shown as 0

Figure 4 presents spot FECa for subjects in the MAD cohorts. Overall, in the MAD cohorts, mean spot FECa remained stable over the trial. Despite the moderate hypercalcemia in the cohorts receiving doses of TransCon ≥20 µg PTH/day, at the time of greatest sCa (~10.5 to 11.2 mg/dL) on Day 11, the urine FECa remained well-controlled below the ULN of the normal range (2%), demonstrating that active PTH within the normal range continuously over 24 hours can enhance the renal handling of calcium.

Detailed information is given in the Investigator's Brochure *Section 5 – Effects in Humans*.

Figure 4: Spot Fractional Excretion of Calcium: MAD Cohorts



[1] Syed 2001

TransCon PTH was generally well tolerated across the clinical dose range proposed for the Phase 2 clinical trial. There were no drug-related serious adverse events (SAEs) or severe adverse events.

In summary, TransCon PTH demonstrated a potent serum calcemic and renal calcium reabsorption effect in normal subjects, predicting control of both sCa and uCa in patients with HP. The effect of TransCon PTH on bone formation markers was consistent with results reported for continuous infusion of PTH(1-34) (Horwitz 2011, Winer 2012, Winer 2014) and lacked an anabolic effect.

A Phase 2 clinical trial [a randomized, placebo-controlled trial to evaluate the safety, tolerability, PD, and PK of TransCon PTH] in patients with HP conducted under GCP, EC, and Declaration of Helsinki guidelines is currently ongoing.

A total of 59 male and female subjects with HP of at least 26 weeks duration treated with a stable dose of ≥0.25 µg BID active vitamin D (or ≥ 1.0 µg/day of alfacalcidol) and ≥400 mg BID calcium for at least 12 weeks prior to Screening were randomized 1:1:1:1 to TransCon PTH 15,

18 or 21 µg/day or to placebo for 4 weeks, followed by an ongoing open-label extension for an additional 12 months. Preliminary data up to 26 weeks of follow up are presently available.

In the per protocol analysis (n=57) at four weeks, 22/44 subjects (50%) in the TransCon PTH group met the primary endpoint vs. 2/13 subjects (15%) in the placebo group with a statistically significant response (p=0.0308). 82% of subjects in the TransCon PTH group were able to come off SoC (i.e., off active vitamin D and ≤ 500 mg/day of calcium supplements) vs 15% of subjects in the placebo group (p<0.0001), and 50% of the TransCon PTH group were able to completely stop active vitamin D and all calcium supplements vs. 0% in the placebo group (p=0.0008). The results demonstrated that TransCon PTH increased sCa levels (see Figure 5), enabled discontinuation of active vitamin D and continuous reduction of calcium supplements over the four-week period. TransCon PTH reduced urinary calcium excretion (as measured by FECa) despite increased sCa resulted in sustained reductions in sP and CxP (see Figure 6).

Figure 5: Albumin adjusted sCa: Absolute Value by Visits

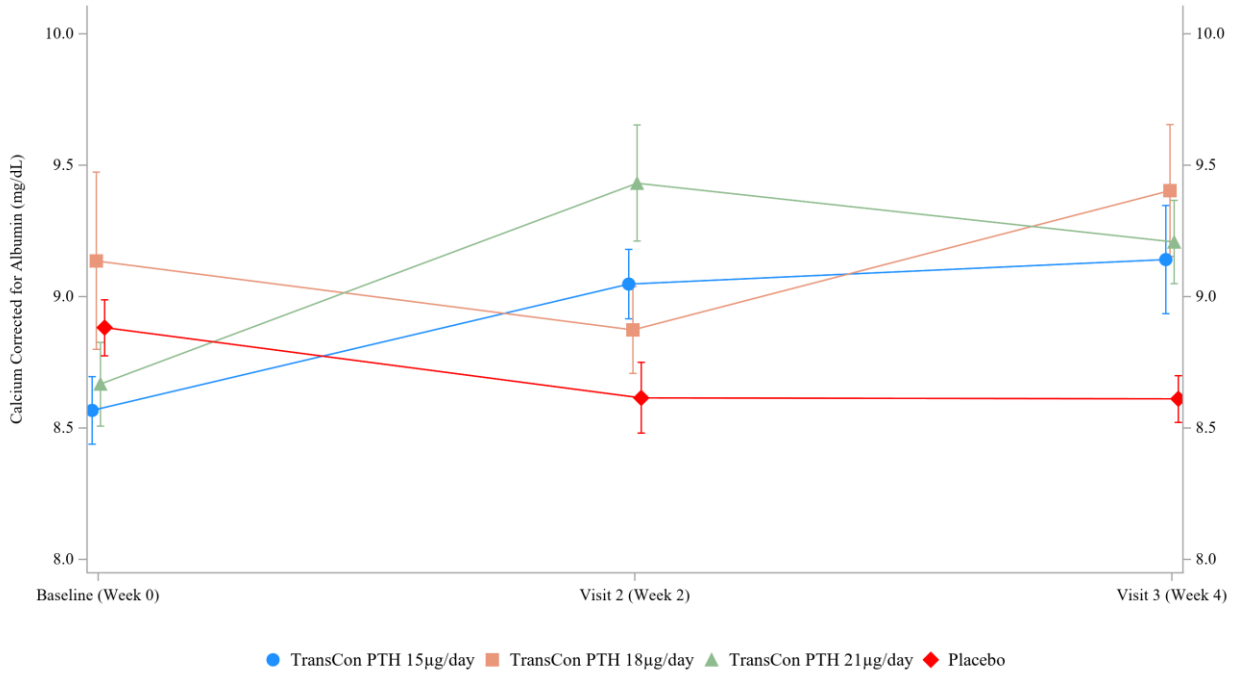
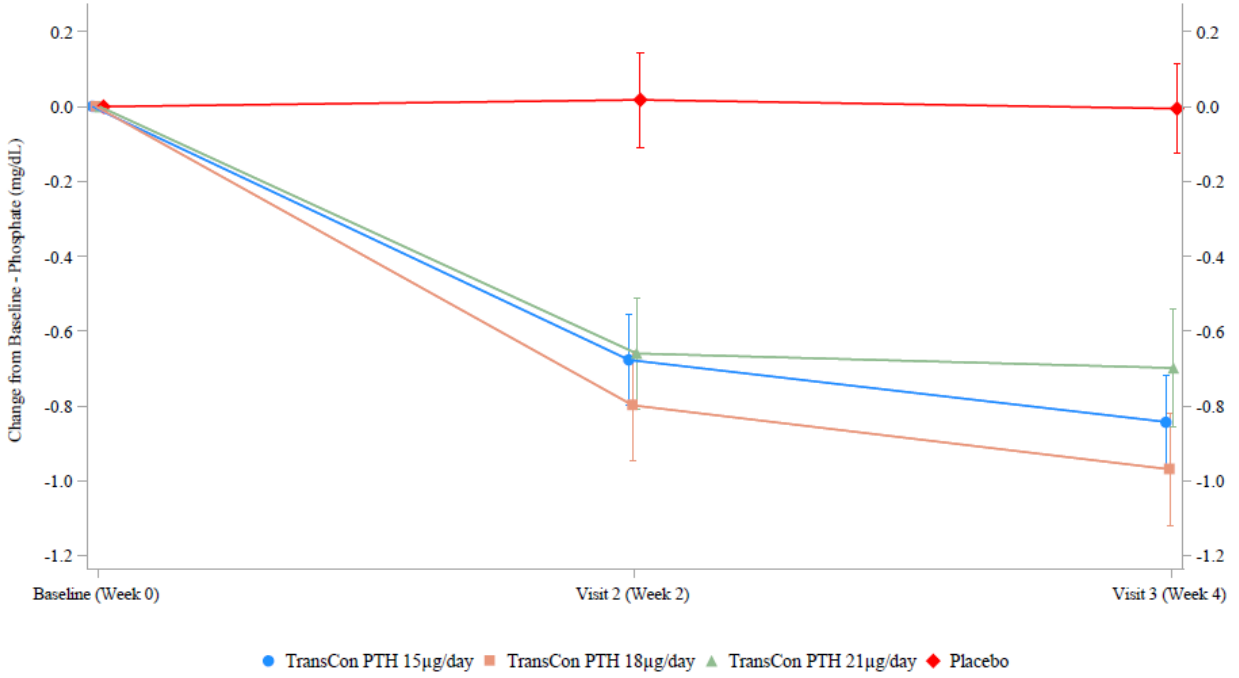


Figure 6: Serum Phosphate: Change from Baseline Value by Visits



All doses were well tolerated within the 4-week Blinded Treatment Period, and no serious or severe adverse events were shown at any point. No treatment-emergent adverse events (TEAEs) led to discontinuation of study drug or early discontinuation of the trial, and the overall incidence of TEAEs was comparable between TransCon PTH and placebo.

Intensive PK assessments (including Free PTH) were analyzed in the Phase 1 trial (TransCon CT-103), showing that the dose range of 12-24 µg/day resulted in Free PTH levels within the lower half of the normal range. Confirmatory PK (including Free PTH in a subset of subjects) was analyzed in the Phase 2 trial (TransCon PTH TCP-201), and again showed that dosing over 4 weeks at doses of 15-21 µg/day resulted in Free PTH levels within the lower half of the normal range.

Thus, the double-blind portion of the Phase 2 trial (TransCon PTH TCP-201) in patients with HP confirms the results of the Phase 1 trial in normal human volunteers, as well as the results of the National Institutes of Health (NIH) PTH-infusion studies (Winer 2012, Winer 2014); namely, that TransCon PTH by providing stable levels of active Free PTH within the physiologic range 24/7 effectively treats all of the acute symptoms and signs of HP more effectively than SoC.

Analysis of data from the Phase 2 open label extension confirm these findings, with 91% of participants requiring no vitamin D and ≤500 mg/d elemental calcium. Participants required TransCon PTH doses between 6 and 39 µg/day. No TEAEs related to abnormal serum calcium have required urgent medical attention. No TEAEs have resulted in discontinuation of study drug, withdrawal from the trial or death. There have been no suspected unexpected serious adverse reactions (SUSARs) as of February 2021. A single participant opted to withdraw consent from the Phase 2 trial in open label Extension Period due to the requirements for contraception.

5.4. TRIAL RATIONALE

A NIH trial with once-daily SC administration of PTH(1-34) maintained the mean sCa level within the normal range over a 24-hour period and reduced uCa excretion (Winer 1996). Another trial in adults demonstrated that twice-daily PTH(1–34), at a significantly lower daily dose, provides improved metabolic control compared with once-daily PTH(1–34) therapy (Winer 1998). Long term effect of PTH(1–34) was further studied in patients with HP of various etiologies. The trial demonstrated that long-term BID PTH administration maintained mean sCa within or just below the normal range over a 3-year period with concurrent normalization of mean urinary calcium excretion (Winer 2003). Further on, a trial comparing continuous PTH(1-34) delivery, by insulin pump, with BID SC injection in adult HP patients showed that continuous exposure to PTH restored bone turnover to normal levels while avoiding the anabolic overstimulation from daily or twice-daily injection (Winer 2012). In addition, pump delivery led to a 65% reduction in the PTH(1-34) dose needed to maintain normal sCa levels in the HP patients. The trial also hypothesized that pump delivery of PTH(1-34) would provide more physiological control of sCa and uCa (compared with conventional treatment or intermittent PTH delivery), would reduce symptoms of HP, improve quality of life (QOL), and lower the long-term risk of renal damage, without adverse effect on bone (Winer 2012).

Recombinant PTH(1-84) (Natpara) was approved as an adjunct to active vitamin D and calcium by the FDA in 2015 to treat HP. But in the Advisory Committee Natpara Briefing Document, the FDA also concluded that due to its short half-life (~ 3 hours), PTH concentrations returns to baseline by 10-12 hours and there is a lack of control of urinary calcium excretion. In addition, Natpara did not reduce the clinical episodes of either hypocalcemia or hypercalcemia compared to placebo plus SoC (Briefing Document 2014). FDA recently published these data (Khurana 2019). Similar comments were made by CHMP (CHMP 2017).

5.5. SUMMARY OF POTENTIAL RISKS AND BENEFITS

5.5.1. Potential Risks

In comparison to short-lived PTH molecules that show supraphysiological PTH levels at t_{max} followed by a rapid decline to undetectable levels after 10-12 hours, TransCon PTH is designed for sustained-release of PTH with a $t_{½}$ of ~ 60 hours, ensuring a stable systemic concentration of the hormone with a flat, infusion-like profile within the physiological normal concentration range. The ability of TransCon PTH to maintain circulating PTH levels in the normal range has been confirmed in a Phase 1 clinical trial (TransCon PTH CT-103) and in the Phase 2 trial (TransCon PTH TCP-201), as well as a lack of an anabolic effect seen with short-lived PTH molecules.

The following risks have been seen in either the TransCon PTH Phase 1 clinical trial or have been reported for approved PTH medications, and thus considered to be potential risks for TransCon PTH:

- Hypercalcemia
- Injection site erythema
- Orthostatic hypotension/presyncope/syncope/dizziness/tachycardia (palpitations)
- Headache

- Fatigue
- Nausea

Osteosarcoma is listed as a potential risk with short-acting PTH analogs, but is not considered to be a risk with TransCon PTH, due to the absence of an anabolic effect based on no increase in procollagen type 1 amino-terminal propeptide (P1NP) over 4 weeks in the Phase 2 trial.

Please refer to the current version of the TransCon PTH Investigator's Brochure *Section 6.4 – Anticipated Risks* for further details.

During the Blinded Treatment Period, there is a potentially increased risk of hypocalcemia if the starting dose of 18 µg/day is sub-optimal, or hypercalcemia if the starting dose of 18 µg/day is higher than optimal for a subject. However, this risk is limited to no more than about 6 days (in the event of hypercalcemia) and about 9 days (in the event of hypocalcemia), when the dose can be held or adjusted up or down, and is also reduced due to the laboratory visits (LVs) over the time between visits. Additionally, acute hypocalcemia can be managed in most situations by PRN doses of active vitamin D and calcium, and acute hypercalcemia can be managed by stopping SoC or by holding the dose of TransCon PTH.

During the reduction in SoC following initiation of study drug (TransCon PTH or placebo) at Visit 1 (and for those subjects on active vitamin D at Visit 10), there is a higher risk of hypocalcemia. However, the following have been included in the protocol to limit the extent of this risk:

- Step-wise decreases of SoC occurring only after sCa levels are confirmed to be within appropriate pre-defined ranges and the subject is asymptomatic
- Returning subjects with symptomatic hypocalcemia to their previous SoC dose
- Allowing subjects who experience hypocalcemic symptoms during this period (and throughout the trial) to use PRN doses of SoC, and to increase their dose of TransCon PTH ≥7 days

5.5.2. Potential Benefits

In the Phase 2 trial, TransCon PTH at doses of 15-21 µg/day allowed subjects with HP to safely discontinue their SoC without experiencing meaningful hypo- or hypercalcemic symptoms, mostly after 2 weeks, along with reductions in FECa by 4 weeks.

6. OBJECTIVES

6.1. PRIMARY OBJECTVE

The primary objective is to assess the treatment effect of daily TransCon PTH on sCa levels, and therapeutic doses of active vitamin D (i.e., calcitriol or alfacalcidol) and calcium at 26 weeks of treatment.

6.2. SECONDARY OBJECTIVES

The secondary objectives are

- To assess the safety and tolerability of daily TransCon PTH
- To assess the treatment effect of daily TransCon PTH on hypoparathyroidism patient experience scale (HPES) domain scores
- To assess the treatment effect of daily TransCon PTH on PD markers (including sCa) and active vitamin D and calcium doses
- To assess the treatment effect of daily TransCon PTH on sP, CxP (albumin-adjusted sCa x sP product) and sMg
- To assess anti-PTH, anti-TransCon PTH and anti-polyethylene glycol (PEG) antibody responses
- To assess the treatment effect during Extension Period
- To assess the treatment effect of daily TransCon PTH on
  - BMD and trabecular bone score (TBS) by DXA
  - Bone turnover markers (serum P1NP and CTx)
- To assess the impact of treatment on patient-reported health-related QOL and a clinician-reported outcome (ClinRO) assessment

6.3. EXPLORATORY OBJECTIVES

CCI

[redacted]

7. TRIAL DESIGN

7.1. TRIAL DESIGN DISCUSSION

The trial design is a randomized, parallel-group, double-blind, placebo-controlled design. Randomization introduces a deliberate element of chance into the assignment of treatment in a clinical trial. During subsequent analysis of the trial data, it provides a sound statistically basis for the quantitative evaluation of the evidence relating to treatment effect.

A double-blind set-up has been chosen to minimize the potential biases resulting from differences in management, treatment, or assignment of subject or interpretation of results that could arise as a result of subjects or investigator knowledge of the assigned treatment.

A placebo group will be used as a control-group. It is considered ethically justifiable since the subjects in both treatment groups can continue taking SoC and PRN medication to treat their hypocalcemic symptoms. Furthermore, subjects will be medically monitored during the trial and the expenses related to SoC may be reimbursed, always following national legislation and/or guidance.

7.2. OVERALL TRIAL DESIGN AND PLAN

The double-blind, placebo-controlled, parallel group treatment period of this trial is expected to enroll approximately 76 subjects from up to approximately 40 sites worldwide.

Subjects will be randomized in a 3:1 ratio into 2 treatment groups:

- TransCon PTH 18 µg/day*, co-administered with SoC
- Placebo for TransCon PTH (excipient solution) 18 µg/day, co-administered with SoC

* *Dose of TransCon PTH refers to dose of PTH(1-34) administered*

Randomization will be stratified by etiology of hypoparathyroidism (post-surgical vs other).

All subjects will start with study drug 18 µg/day of and will be individually and progressively titrated to an optimal dose in dose increments of 3 µg/day.

Study drug, calcium and active vitamin D will be titrated according to the Titration Algorithm (Appendix 2) on each occasion serum calcium is measured.

Dose range for the trial will be supported by 3 pen presentations delivering discrete doses of 6, 9, and 12 µg/day; 15, 18, and 21 µg/day; and 24, 27 and 30 µg/day, respectively. The TransCon PTH allowed dose range will be 6-60 µg/day.

Following successful completion of the Blinded Treatment Period, subjects will be allowed to enter the open-label Extension Period when all subjects will receive TransCon PTH.

Because the potential for TransCon PTH to be a hormone replacement therapy is being assessed in this trial, a goal is for subjects to achieve independence from standing doses of calcitriol and alfacalcidol, and to progressively reduce calcium supplements to ≤600 mg/day (a dose considered as "supplemental" to meeting recommended daily intake for general health, as opposed to a "therapeutic" dose to treat HP). The progressive cessation of calcitriol, alfacalcidol, and calcium should occur while increasing the dose of TransCon PTH to achieve normocalcemia.

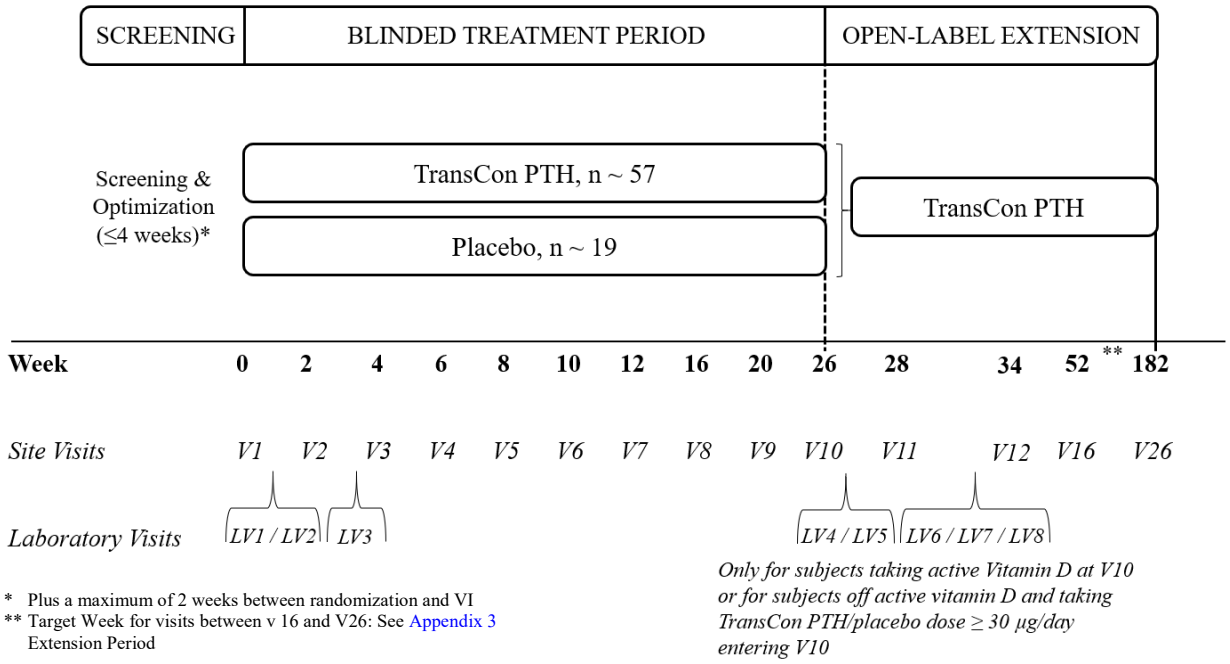
Per the Schedule of Events, initial study visits and LVs occur relatively frequently to accommodate dose titration of TransCon PTH, and occur less frequently later on (see Appendix 3 and Appendix 4).

The trial consists of:

- **Screening Period (supplement optimization):** Up to approximately 4 weeks (plus a recommended period of up to approximately 2 weeks between randomization and Visit 1)
- **Blinded Treatment Period (study drug and SoC optimization):** 26 weeks
- **Extension Period (open-label TransCon PTH treatment):** 156 weeks

The total duration of participation for each subject is expected to last up to approximately 190 weeks (including follow up telephone contact 2 weeks after last study drug administration).

Figure 7: Trial Design



7.2.1. Measures Taken to Maximize Study Integrity and Minimize Bias

Subject visits should be performed at approximately the same time of day, and preferably in the morning hours. Also, assessments should be performed in a similar fashion at each visit. Additionally, all efforts will be made to keep missing data to a minimum, including the following:

- Investigators will be trained about the importance of subject retention
- Investigators will be instructed to encourage subjects to complete all trial visits, including any subjects who discontinue the study drug early
- The Informed Consent Form (ICF) will include a statement educating subjects about the scientific importance of their data even if the subject discontinues study drug early
- Special efforts will be made to provide assistance to subjects/families who might discontinue due to travel or cost barriers, such as offers of free transportation to the clinic
- All trial visits have visit windows to allow flexibility for clinic attendance (see Schedule of Events, Appendix 3)
- Every effort will be made to contact subjects or other family members to maintain contact with the clinic
- To minimize individual investigator bias, Appendix 2 provide standardized guidelines for withdrawal/adjustment of SoC and titration of TransCon PTH based on objective laboratory tests and subjects' experience of hypo- or hypercalcemic symptoms. Additionally, the Medical Monitor will perform timely review of albumin-adjusted sCa and/or ionized sCa results and prescribed dosing to confirm investigator compliance with Appendix 2

7.3. TRIAL SITES

The trial will be conducted at up to approximately 40 sites. All centers will be specialized treatment centers in the management of HP.

8. TRIAL POPULATION

Approximately 76 male and female adults with postsurgical chronic HP or autoimmune, genetic, or idiopathic HP, for at least 26 weeks; treated with either calcitriol ≥0.5 µg/day or alfacalcidol ≥1.0 µg/day and elemental calcium ≥800 mg/day for at least 12 weeks prior to Screening; and have a 24-hour uCa excretion ≥125 mg/24 hr, may enter the Screening Period.

Note: The thresholds for calcitriol, alfacalcidol, and calcium are provided above in total daily doses. Acknowledging that the total daily doses may be taken in divided doses throughout the day, the corresponding thresholds would be calcitriol ≥0.25 µg BID; alfacalcidol ≥0.50 µg BID; calcium ≥400 mg BID.

8.1. TRIAL ENTRY CRITERIA

8.1.1. Inclusion Criteria

1. Males and females, ≥18 years of age
2. Subjects with postsurgical chronic HP, or auto-immune, genetic, or idiopathic HP for at least 26 weeks. Diagnosis of HP is established based on a history of hypocalcemia in the setting of inappropriately low serum PTH levels (Hypocalcemia is defined as a value below the reference range for normal at the performing laboratory. Inappropriately low serum PTH levels are defined as at or below the median value of the reference range for normal at the performing laboratory while the concomitant serum calcium is low. If specific lab results at the time of original diagnosis are not available, as historical diagnosis affirming these two components is adequate for inclusion)
3. Requirement for doses of SoC (e.g., calcitriol, alfacalcidol, calcium supplements) at or above a minimum threshold:
    - ***For countries other than Japan***: requirement for a dose of calcitriol ≥0.5 µg/day, or alfacalcidol ≥1.0 µg/day and (elemental) calcium ≥800 mg/day (e.g., calcium citrate, calcium carbonate etc.) for at least 12 weeks prior to Screening*. In addition, the dose of calcitriol, or alfacalcidol, or calcium should be stable** for at least 5 weeks prior to Screening
    - ***For Japan****:* requirement for a dose of calcitriol ≥1.0 µg/day, or alfacalcidol ≥2.0 µg/day for at least 12 weeks prior to Screening*. In addition, the dose of calcitriol or alfacalcidol should be stable** for at least 5 weeks prior to Screening. In Japan only (due to local practice and dietary patterns), there is no requirement to exceed a minimum dose of calcium supplements

** Excluding individuals receiving PTH-like drugs within 12 weeks of the screening visit, who need only demonstrate a stable requirement for elemental calcium and active vitamin D above minimum thresholds for 5 weeks prior to the screening visit.*

*** Does not preclude occasional (≤2/week) PRN doses of calcium and/or active vitamin D for symptomatic hypocalcemia*

4. Optimization of supplements prior to randomization to achieve the target serum levels of:
    - 25(OH) vitamin D levels of 20-80 ng/mL (49-200 nmol/L) and
    - Magnesium level in the normal range, or just below the normal range i.e.: ≥1.3 mg/dL (0.53 mmol/L) and
    - Albumin-adjusted or ionized sCa level in the normal range, or *just below the normal range, i.e.:
        - Albumin-adjusted sCa 7.8-10.6 mg/dL (or 1.95-2.64 mmol/L)
        - Ionized sCa 4.40-5.29 mg/dL (or 1.10-1.32 mmol/L)

** Just below the normal range implies the numerical range of 7.8-8.2 mg/dL (or 1.95-2.06 mmol/L) for albumin-adjusted sCa and the numerical range of 4.40-4.636 mg/dL (or 1.10-1.159 mmol/L) for ionized sCa.*

5. The subject demonstrates a 24-hour uCa excretion of ≥125 mg/24h (on a sample collected within 52 weeks prior to Screening or during the Screening Period)

    Note: Although 24-hour urine samples prior to Screening may be done on or off thiazide therapy, thiazide therapy is prohibited during the trial; and the 24-hour urine collection scheduled prior to Visit 1 must be done while off thiazides for at least 4 weeks prior to collection
6. BMI 17- 40 kg/m^2 at Screening
7. If ≤25 years of age, radiological evidence of epiphyseal closure based on X-ray of non-dominant wrist and hand
8. Thyroid-stimulating hormone (TSH) within normal laboratory limits within the 6 weeks prior to Visit 1; if on suppressive therapy for a history of thyroid cancer, TSH level must be ≥0.2 mIU/L
9. If treated with thyroid hormone replacement therapy, the dose must have been stable for at least 5 weeks prior to Screening
10. eGFR ≥30 mL/min/1.73 m^2 during Screening
11. Able to perform daily SC self-injections of study drug (or have a designee to perform injections) via a pre-filled injection pen
12. Able and willing to provide written and signed ICF in accordance with GCP
13. For France **only**: The subject is obligated to be affiliated with, or beneficiary of a social security system or assimilated.

8.1.2. Exclusion Criteria

1. Impaired responsiveness to PTH (pseudohypoparathyroidism) which is characterized as PTH-resistance, with elevated PTH levels in the setting of hypocalcemia
2. Any disease that might affect calcium metabolism or calcium-phosphate homeostasis or PTH levels other than HP, such as active hyperthyroidism; Paget disease of bone; severe hypomagnesemia; type 1 diabetes mellitus or poorly controlled type 2 diabetes mellitus (HbA1C >9%, documented HbA1C result drawn within 12 weeks prior to Screening is acceptable); severe and chronic liver, or renal disease; Cushing syndrome; multiple myeloma; active pancreatitis; malnutrition; rickets; recent prolonged immobility; active

malignancy (other than low-risk well differentiated thyroid cancer or non-melanoma skin cancer); active hyperparathyroidism; parathyroid carcinoma within 5 years prior to Screening; acromegaly; or multiple endocrine neoplasia types 1 and 2

3. High risk thyroid cancer within 2 years, requiring suppression of TSH <0.2 mIU/L
4. Use of loop diuretics, phosphate binders (other than calcium supplements), digoxin, lithium, methotrexate, biotin >30 µg/day, or systemic corticosteroids (other than as replacement therapy)
5. Use of thiazide diuretic within 4 weeks prior to the 24-hour urine collection scheduled to occur within 1 week prior to Visit 1
6. Use of PTH-like drugs (whether commercially available or through participation in an investigational trial), including PTH(1-84), PTH(1-34), or other N-terminal fragments or analogs of PTH or PTH-related protein, within 4 weeks prior to Screening
7. Use of other drugs known to influence calcium and bone metabolism, such as calcitonin, fluoride tablets (>0.5 mg/day), strontium, or cinacalcet hydrochloride, within 12 weeks prior to Screening
8. Use of osteoporosis therapies known to influence calcium and bone metabolism, i.e., bisphosphonate (oral or intravenous [IV]), denosumab, raloxifene, or romosozumab therapies within 2 years prior to Screening
9. Non-hypocalcemic seizure disorder with a history of a seizure within 26 weeks prior to Screening

   Note: History of seizures that occur in the setting of hypocalcemia is not exclusionary
10. Increased risk for osteosarcoma, such as those with Paget's disease of bone or unexplained elevations of alkaline phosphatase, hereditary disorders predisposing to osteosarcoma, or with a prior history of substantial external beam or implant radiation therapy involving the skeleton
11. Pregnant or lactating women

    Note: Acceptable highly effective contraception (see Appendix 1) is required for sexually active women of childbearing potential during the trial and for 2 weeks after the last dose of study drug, and pregnancy testing will be performed throughout the trial. Sexually active women of childbearing potential who are unwilling to use acceptable highly effective contraception are excluded from the trial
12. Male who has a female partner who intends to become pregnant or is of childbearing potential and is unwilling to use adequate contraceptive methods during the trial

    Note: Male subjects must use a condom, or his female partner of childbearing potential must use an effective form of contraception (as per CTFG definition), from the beginning of screening to the last trial visit
13. Diagnosed drug or alcohol dependence within 3 years prior to Screening
14. Disease processes that adversely affect gastrointestinal absorption, including but not limited to short bowel syndrome, significant small bowel resection, gastric bypass, tropical sprue,

active celiac disease, active ulcerative colitis, active Crohn's disease, gastroparesis and AIRE gene mutations with malabsorption

15. Chronic or severe cardiac disease within 26 weeks prior to Screening including but not limited to congestive heart failure, myocardial infarction, severe or uncontrolled arrhythmias, bradycardia (resting heart rate <48 beats/minute, unless chronic and asymptomatic), symptomatic hypotension or systolic BP <80 mm Hg or diastolic <40 mm Hg or poorly controlled hypertension (systolic BP >165 mm Hg or diastolic >95 mm Hg). In the absence of a prior history of hypertension, an isolated BP >165/95 in the setting of white coat hypertension/anxiety may not be exclusionary and a measurement can be repeated prior to randomization
16. Cerebrovascular accident within 5 years prior to Screening
17. Within 26 weeks prior to Screening: acute colic due to nephrolithiasis, or acute gout. Subjects with asymptomatic renal stones are permitted
18. Participation in any other interventional trial in which receipt of investigational drug or device occurred within 8 weeks (or within 5.5 times the half-life of the investigational drug) (whichever comes first) prior to Screening
19. Any disease or condition that, in the opinion of the investigator, may require treatment or make the subject unlikely to fully complete the trial, or any condition that presents undue risk from the investigational product or procedures, including treated malignancies that are likely to recur within the approximate 3.5-year duration of the trial
20. Known allergy or sensitivity to PTH or any of the excipients [metacresol, mannitol, succinic acid, NaOH/(HCl)]
21. Likely to be non-compliant with respect to trial conduct
22. Any other reason that in the opinion of the investigator would prevent the subject from completing participation or following the trial schedule

8.2. SUBJECT WITHDRAWAL/DISCONTINUATION

A subject may withdraw from the study at any time at his/her own request or may be discontinued at any time at the discretion of the investigator for safety, behavioral, or compliance reasons. This is expected to be uncommon.

Additionally, the investigator may discontinue the treatment of a subject at any time if considered to be in the subject's best interest.

In the case of subject discontinuation, the investigator should schedule an Early Termination Visit to collect data, particularly AE follow-up data (if applicable), and to collect blood for final laboratory evaluations. This visit should contain all appropriate assessments and the reason(s) for trial discontinuation should be documented, see Section 10.1.8. Individual assessments may be waived if the subject refuses to participate, if they have been done recently and/or are not deemed appropriate or required. Such instances shall be discussed with the Medical Monitor. For subjects that discontinue study drug for reasons related to safety, unblinding of the treatment assignment for the subject may occur if deemed necessary by the Sponsor to assess a potential safety signal or by the investigator to provide adequate medical care to the subject.

The investigator/site staff should make every attempt to contact the subject via phone to arrange the appropriate follow-up assessment(s) for such subjects.

Data obtained until trial discontinuation will be used in the statistical analyses.

See Section 10.1.8 for details on Early Termination Visit.

8.2.1. Study Drug Discontinuation

8.2.1.1. Study Drug Discontinuation during Blinded Treatment Period

Unless informed consent is withdrawn*, subjects who permanently discontinue study drug during the Blinded Treatment Period should:

- Attend all subsequent visits within the Blinded Treatment Period
- Complete an Early Termination Visit in place of Visit 10
- Not continue into the Extension Period

All efforts should be made for subject to continue in the Blinded Treatment Period even if study drug is discontinued.

* *If the subject is not willing to attend all subsequent trial visits within the Blinded Treatment Period, this should be considered a withdrawal of consent and an Early Termination Visit should be scheduled.*

See Section 10.1.8 on Early Termination Visit.

8.2.1.2. Study Drug Discontinuation during Extension Period

Subjects who permanently discontinue study drug during the Extension Period should be withdrawn from the trial and an Early Termination Visit should be scheduled immediately.

See Section 10.1.8 for details on Early Termination Visit.

9. TREATMENTS

9.1. INVESTIGATIONAL PRODUCT

TransCon PTH drug product is supplied as a solution with a concentration of 0.3 mg PTH(1-34)/mL in a single-patient-use prefilled pen intended for SC injection. Excipients include metacresol, mannitol, succinic acid, and NaOH/(HCl). The prefilled pens are stored in the refrigerator until first use; the TransCon PTH drug product is stable at room temperature below 86°F (30°C) for the 14 days in-use period when dosing with the pre-filled pen.

Three presentations of the prefilled pen containing TransCon PTH drug product and the three pen presentations are 6, 9, and 12 µg/day; 15, 18, and 21 µg/day; and 24, 27 and 30 µg/day, respectively.

Refer to the Investigator's Brochure *Section 3 – Physical, Chemical, and Pharmaceutical Properties and Formulations* for details on the composition and characteristics of TransCon PTH and the Pharmacy Manual and instructions for use (IFU) for complete details on storage and handling.

9.1.1. Reference Product

The placebo for TransCon PTH drug product (excipient solution in the pens) are in three pen presentations to mimic dose ranges of 6, 9, and 12 µg/day; 15, 18, and 21 µg/day; and 24, 27 and 30 µg/day within the Blinded Treatment Period.

9.1.2. Labeling

All study drug will be labeled according to current Good Manufacturing Practice and local regulatory requirements. The labels carry unique identification pack numbers. Subjects will be provided with dosing and storage instructions.

9.1.3. Accountability, Storage, and Dispensing

Investigator or delegated site staff will be responsible for study drug, ancillary supplies, and associated procedures, exercising accepted medical and pharmaceutical practices.

Study drug must be kept in a locked, temperature-controlled, and temperature-monitored area with access limited to designated trial staff and stored according to its labeling. Investigator or dedicated trial staff must evaluate the storage temperature and inform Sponsor immediately if study drug has been stored outside the specified conditions on the label. The trial will use an internet-based interactive response technology (IRT) system as source to capture drug inventory and accountability data, including receipt of drug inventory and supplies by the site, treatment assignment for each subject, dispensing to subjects, return to the site from subjects, and return to the contracted parties (or destruction with the Sponsor's approval). The IRT system complies with all applicable regulatory requirements for record keeping and record retention in clinical trials [21 CFR Part 11 and ICH E6 (R2) GCP].

Direct-to-subject shipments of study drug from investigational sites will be allowed in exceptional cases in which subjects might not be able to attend on-site visits and risk continued access to study drug for subjects.

Investigator or delegated site staff will be responsible for study drug/pen accountability and reconciliation of study drug.

Site staff will provide training on proper storage and study drug administration to each subject at Visit 1. This training will include a review of the IFU and on-site administration of the first dose of study drug by the subject. A copy of the IFU will be provided to the subject for reference at home.

Note: Under no circumstances will the investigator allow study drugs to be used other than as directed by this protocol.

See Pharmacy Manual and IFU for further details.

9.1.4. Post-trial Treatment

After the end of the trial, the investigator must advice trial subject on access to appropriate and available treatment. Such treatment will not be funded by Sponsor.

9.2. TREATMENT ADMINISTERED

The TransCon PTH delivery system consists of a multi-use cartridge integrated into a modified Ypsomed UnoPen Fix pen injector using 31Gx5 mm pen needles. The cartridge contains compounded solution of TransCon PTH or placebo for TransCon PTH with a fill volume sufficient for 14 doses. Each study drug administration is in a volume ≤100 µL (6 µg/day in volumes of 20 µL, 9 µg/day in volumes of 30 µL, 12 µg/day in volumes of 40 µL, 15 µg/day in volumes of 50 µL, 18 µg/day in volumes of 60 µL, 21 µg/day in volumes of 70 µL, 24 µg/day in volumes of 80 µL, 27 µg/day in volumes of 90 µL, or 30 µg/day in volumes of 100 µL), and is to be self-administered (following training by study staff). There is a total of 4 possible injection areas: right abdomen, left abdomen, right anterior thigh, and left anterior thigh, and multiple sub-areas within each area. Subjects should be instructed to rotate injection sites. Refer to the IFU for complete instructions on administration.

Although the starting dose is 18 µg PTH or placebo (using the mid-dose pen), throughout the entire trial (including Blinded and Open Label Treatment Period), all three pen presentations are available for TransCon PTH or corresponding placebo allowing for dose increments of 3 µg (6, 9, and 12 µg; 15, 18, and 21 µg; and 24, 27 and 30 µg, respectively).

The study drug allowed dose range will be 6-60 µg/day. All doses >30 µg/day will be delivered in the form of two single doses injected one after another at different injection sites using two pens of the same pen presentation, except for the 45 µg/day dose which will be delivered as a combination of the mid-dose and high-dose pen presentations as shown in Table 1. Based on the design verification data for the pen presentations (at standard atmosphere conditions), dose accuracy data for a given combination of doses from two pens has been evaluated against the acceptance criteria for dose accuracy. The combinations presented in Table 1 will deliver the desired doses within the specifications for dose accuracy. Two injections will be given shortly after each other and the dose can therefore be considered the sum of the two injections.

Table 1: Recommended Dosing Schemes >30 µg PTH(1-34)/Day or Placebo

Dose	Dosing Scheme	Pen Combination
33 µg/day	18 µg/day + 15 µg/day	Two mid-dose pens
36 µg/day	18 µg/day + 18 µg/day	Two mid-dose pens
39 µg/day	21 µg/day + 18 µg/day	Two mid-dose pens
42 µg/day	21 µg/day + 21 µg/day	Two mid-dose pens
45 µg/day	24 µg/day + 21 µg/day	Mid-dose and high-dose pens
48 µg/day	24 µg/day + 24 µg/day	Two high-dose pens
51 µg/day	27 µg/day + 24 µg/day	Two high-dose pens
54 µg/day	27 µg/day + 27 µg/day	Two high-dose pens
57 µg/day	30 µg/day + 27 µg/day	Two high-dose pens
60 µg/day	30 µg/day + 30 µg/day	Two high-dose pens

9.3. SELECTION OF TRIAL DOSES

The 4-week Blinded Treatment Period of the Phase 2 trial - with fixed dosing of TransCon PTH 15, 18, and 21 µg/day - demonstrated that a dose of 18 µg/day was both effective and well-tolerated, with less hypercalcemia compared to a dose of 21 µg/day and without meaningful hypocalcemia. Preliminary data from the open label extension of the Phase 2 trial as of February 2021 demonstrates comparable safety profiles at doses of both 15 and 18 µg/day. The dose distribution during the open label extension has been 6-39 µg/day, titrated to achieve normocalcemia. Phase 2 data demonstrates no meaningful difference in AEs, including those related to hypo- or hypercalcemia, on TransCon PTH doses <15 µg/day or >21 µg/day. 5-10% of participants are anticipated to require doses >30 µg/d to achieve normocalcemia in the present trial. Therefore, the starting dose for the Blinded Treatment Period will be 18 µg/day, followed by titration to 6-60 µg/day to achieve normocalcemia and independence from conventional therapy.

9.4. TREATMENT ASSIGNMENT

9.4.1. Treatment Assignment During Blinded Treatment Period

Subjects will be randomized 3:1 into TransCon PTH or placebo.

- TransCon PTH 18 µg/day, co-administered with SoC
- Placebo for TransCon PTH, co-administered with SoC
  - Mimicking dose of 18 µg/day

All subjects will start with study drug 18 µg/day and will be individually and progressively titrated to an optimal dose in dose increments of 3 µg/day.

9.4.2. Treatment Assignment During Open-Label Extension Period

At Visit 10 (Week 26), subjects will be assigned to open-label treatment as follows:

- **If still taking active vitamin D:** Start TransCon PTH at a dose of 18 µg/day, and subsequently follow the titration algorithm as per Appendix 2
- **If NOT taking active vitamin D:**
  - **And taking study drug ≥30 µg/day:** Start TransCon PTH at a dose of 18 µg/day, and subsequently follow the titration algorithm per Appendix 2
  - **And taking study drug <30 µg/day:** Start TransCon PTH at the same dose of study drug taken at the end of the Blinded Treatment Period. Exception: in cases of an out-of-range sCa level at Visit 10, adjust the TransCon PTH and/or calcium doses as per Appendix 2

9.5. DOSE ADJUSTMENTS

9.5.1. Screening Period Supplement Dose Adjustments

During the Screening Period, adjustments to doses of HP-related supplements [SoC (active vitamin D – calcitriol, alfacalcidol – and calcium), magnesium, vitamin D] will be made to achieve the following laboratory levels:

- 25(OH) vitamin D: 20-80 ng/mL (49-200 nmol/L)
- Magnesium within the normal range or just below the normal range i.e.: ≥1.3 mg/dL (0.53 mmol/L)
- Albumin-adjusted or ionized sCa: within the normal range, or just below the normal range, i.e.:
  - Albumin-adjusted sCa 7.8-10.6 mg/dL (or 1.95-2.64 mmol/L)
  - Ionized sCa 4.40-5.29 mg/dL (or 1.10-1.32 mmol/L)

Therapeutic doses of calcitriol, alfacalcidol, calcium, magnesium and vitamin D3 are adjusted only after initial Screening laboratory results are received. Follow-up laboratory assessments of the above values, with exception of 25(OH) vitamin D levels, are performed approximately 3 days after every dose adjustment during the Screening Period. 25(OH) vitamin D level may be rechecked ≥7 days from any dose change. If required, additional dose adjustments, with follow-up laboratory assessments approximately 3 days later, may be performed throughout the Screening Period.

9.5.2. Blinded Treatment Period (Visits 1-10; Weeks 0-26) Dose Adjustments

9.5.2.1. SoC Dose Adjustments during Blinded Treatment Period

Visit 1: Start study drug 18 µg/day **and** decrease active vitamin D dose by 33-50% (e.g., skip 2nd dose of the day if taking BID, skip final dose of the day if taking three times daily (TID), or reduce once daily dose of alfacalcidol ≥1.0 µg by 50% (≥0.5 µg).

Subsequently, active vitamin D and/or calcium doses should be titrated as per Appendix 2. The target vitamin D range during treatment phases of this trial is 30-80 ng/mL

SoC adjustments should be made preferably within 48 hours of blood collection.

Because this trial is assessing the potential for TransCon PTH to be a parathyroid hormone replacement therapy, a goal is for subjects to achieve independence from standing doses of calcitriol, alfacalcidol, and calcium supplements.

Note: In case needed to meet recommended dietary intake of calcium, it is permitted to take calcium supplements ≤600 mg/day as a nutritional supplement for the sake of reaching the recommended dietary intake. The calcium dose of ≤600 mg/day is considered as "supplemental" to meeting recommended daily intake for general health, as opposed to a "therapeutic" dose to treat hypoparathyroidism. The progressive cessation of calcitriol, alfacalcidol, and calcium should occur while increasing the dose of TransCon PTH to achieve normocalcemia.

9.5.2.2. Study Drug Dose Adjustments During Blinded Treatment Period

All subjects will start with 18 µg/day of study drug. The study drug dose will be individually and progressively titrated in dose increments of 3µg/day with the goal to achieve normocalcemia as shown in Appendix 2.

Study drug doses can be increased by 3 µg/day as long as ≥7 days have elapsed since a prior dose adjustment in study drug. Gradual increases in study drug doses may facilitate gradual reduction and eventual cessation of SoC. Alternatively, study drug doses can be decreased by

3 µg/day for serum calcium levels that continue to be high even after all SoC has been withdrawn.

Serum calcium results from local laboratory analysis will be used to guide titration of study drug. Central laboratory results will be definitive for data analysis.

9.5.3. Extension Period (Visits 10+; Weeks 26+) Dose Adjustments

9.5.3.1. SoC Dose Adjustments during Extension Period

At Visit 10 (Week 26), the following categories of subjects will start TransCon PTH 18 µg/day.

- Those still taking active vitamin D (this group may be enriched with subjects initially randomized to placebo)
- Those off active vitamin D and taking study drug ≥30 µg/day

As such, when selecting the appropriate doses of SoC (active vitamin D and calcium supplements) to accompany the TransCon PTH 18 µg/day, investigators are advised to:

- Consider the doses of active vitamin D and calcium required at trial baseline (before exposure to the study drug)

AND

- Reduce the active vitamin D (taken before exposure to study drug) by 33-50% when starting TransCon PTH 18 µg/day at Visit 10

Start the new SoC regimen:

- On the day ***of*** Visit 10 for those subjects who are still taking active vitamin D at the time of Visit 10
- On the day ***after*** Visit 10 for those subjects who are off active vitamin D and taking study drug ≥30 µg/day at Visit 10

9.5.3.2. TransCon PTH Dose Adjustments during Extension Period

For subjects still taking active vitamin D at Visit 10: Start TransCon PTH at a dose of 18 µg/day at Visit 10, and subsequently follow the titration algorithm as per Appendix 2.

For subjects not taking active vitamin D at Visit 10 and taking study drug dose ≥ 30 µg/day: Start TransCon PTH at a dose of 18 µg/day at Visit 10, and subsequently follow the titration algorithm per Appendix 2.

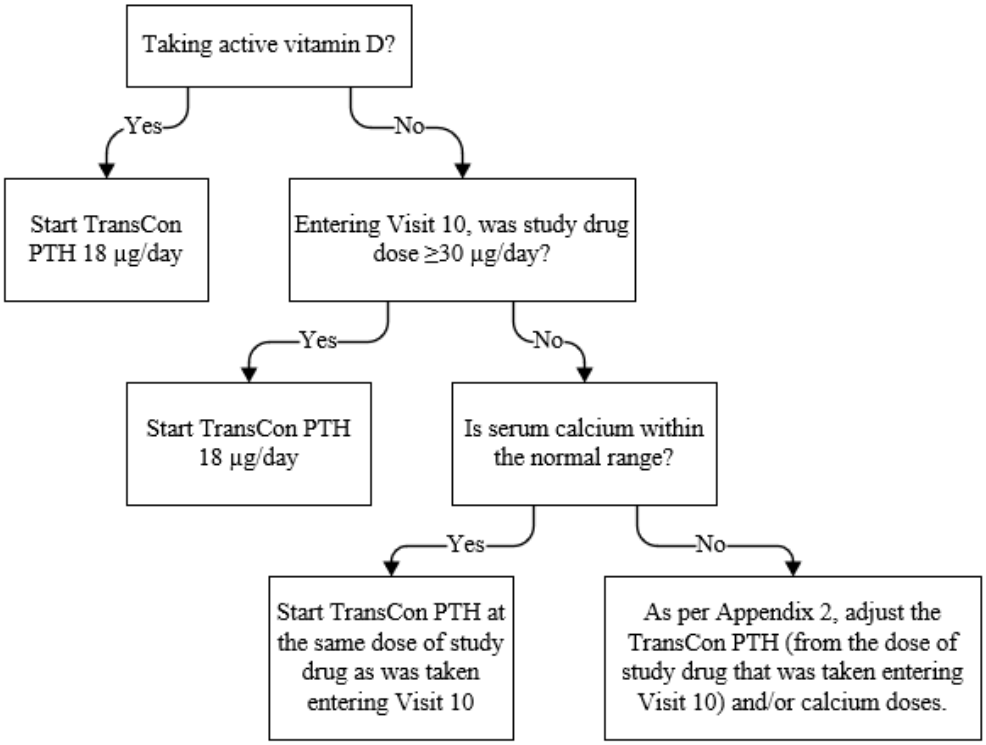
For subjects not taking active vitamin D at Visit 10 and taking study drug dose < 30 µg/day: Start TransCon PTH at Visit 10 at the same dose of study drug taken at the end of the Blinded Treatment period. Exception: in cases of an out-of-range sCa level at Visit 10, adjust the TransCon PTH and/or calcium doses as per Appendix 2.

The TransCon PTH dose selection at Visit 10 is also demonstrated in the decision tree below in Figure 8.

TransCon PTH doses can be increased by 3 µg/day as long as ≥7 days have elapsed since a prior dose adjustment in study drug. Gradual increases in TransCon PTH doses may facilitate gradual reduction and eventual cessation of SoC. Alternatively, TransCon PTH doses can be decreased

by 3 µg/day for serum calcium levels that continue to be high even after all SoC has been withdrawn.

Figure 8: Decision Tree for TransCon PTH Dose Selection at Visit 10 (Week 26)



9.6. STUDY DRUG DOSE CHANGES, INTERUPTIONS, OR STOPPING

9.6.1. Dose changes and Treatment Interruptions

The investigator may change the dose, and/or temporarily hold the study drug for an individual subject as per the dose titration algorithm (Appendix 2).

The investigator will determine dose changes and/or study drug holding/stopping for the following situations:

- Persistent ***hypocalcemia*** with albumin-corrected serum calcium <8.3 mg/dL[1] for >7 days despite all of the following:
  - increases in doses of (and adherence to) study drug, calcium supplements, and active vitamin D
  - maximum protocol permitted dose of study drug

[1] Thresholds for albumin-corrected serum calcium: <8.3 mg/dL (<2.07 mmol/L), or ionized calcium: <1.16 mmol/L

- Persistent ***severe hypocalcemia*** with albumin-corrected serum calcium <7.0 mg/dL[2] for >7 days despite:
  - increases in (and adherence to) study drug, calcium supplements, and active vitamin D
  - medical intervention (e.g. intravenous calcium infusions, urgent/emergency care, hospitalization) as needed and at the discretion of the investigator
- Persistent ***hypercalcemia*** with albumin-corrected serum calcium >10.6 mg/dL[3] for >7 days despite all of the following:
  - cessation of active vitamin D and calcium supplements
  - study drug dose 6 µg/day
- Persistent ***severe hypercalcemia*** with albumin-corrected serum calcium ≥12.0 mg/dL[4] for >7 days despite:
  - cessation of active vitamin D and calcium supplements
  - decreases in/cessation of study drug
  - oral hydration
  - medication intervention (e.g. intravenous fluids, urgent/emergency care, hospitalization) as at the discretion of the investigator
- Persistent vasodilatory symptoms that cannot be corrected with adjustments to study drug
- Any other study-drug related severe adverse event, or serious adverse event, that warrants holding or discontinuing study drug at the discretion of the investigator and/or medical monitor
- "Non-responders" to TransCon PTH may be evaluated for discontinuation of TransCon PTH therapy, after a discussion between the investigator and medical monitor during the open label Extension Period of the trial
  - A "non-responder" to TransCon PTH is a subject taking the maximum dose of TransCon PTH 60 µg/day for at least 39 weeks, who is unable to reduce standing or as-needed doses of SoC as compared to his/her baseline requirements for conventional therapy (i.e. has symptoms and/or low serum calcium if conventional therapy is reduced below study baseline requirements). If reduction in conventional therapy remains impossible at the end of 39 weeks, the patient may discontinue TransCon PTH. The selection of a 39-week duration recognizes there may be rare instances where subjects temporarily have significantly accelerated clearance of TransCon PTH that is expected to spontaneously resolve by approximately 26-35 weeks (and thus be associated with a reduction in a subject's dose requirement of TransCon PTH)

[2] Thresholds for albumin-corrected serum calcium: <7.0 mg/dL (<1.75 mmol/L), or ionized calcium: <0.95 mmol/L
[3] Thresholds for albumin-corrected serum calcium: >10.6 mg/dL (>2.64 mmol/L), or ionized calcium: >1.32 mmol/L
[4] Thresholds for albumin-corrected serum calcium: ≥12.0 mg/dL (≥3.00 mmol/L), or ionized calcium: ≥1.50 mmol/L

Persistent severe hypocalcemia and persistent severe hypercalcemia (as defined above) will be reported to the regulatory authorities, based on local requirements.

See Section 8.2.1 for further guidance on study drug discontinuation.

9.6.2. Required Stopping

The investigator, with Sponsor medical monitor notification, must stop the study drug for an individual subject at any time during the trial in the presence of the following:

- Evidence of a severe hypersensitivity to TransCon PTH
- Confirmed neutralizing anti-PTH antibodies that correlate with reduced PD response
- Suspicion of osteosarcoma (e.g., persistent localized pain or occurrence of a new soft tissue mass tender to palpation that could be consistent with osteosarcoma, in association with an elevation of bone-specific alkaline phosphatase)
- Pregnancy

Ascendis medical monitors will immediately notify the Data Monitoring Committee (DMC) and Ascendis pharmacovigilance of any such events for evaluation of potential broader safety concerns

9.7. TREATMENT COMPLIANCE

Compliance of both study drug and SoC doses will be assessed based on review of the subject diary and returned pens at every clinic visit.

9.8. STANDARD OF CARE

SoC will not be provided by the Sponsor acknowledging the preferred and prescribed type of calcium salt, active vitamin D analog, and ratio of calcium to active vitamin D may differ among prescriber, patient, and global region (Babey 2018). For example, the prescribed active vitamin D or analog and calcium salt may be based on prescriber/individual subject/local preference and availability. The calcium salts are known to differ with respect to ease of absorption, requirement of gastric acid for absorption, content (percentage) of elemental calcium - and thus size of tablet. Finally, the proportions of active vitamin D to calcium supplements may also differ based on local practice and diet patterns, and effects on individual subject. Thus, calcium and active vitamin D regimens are highly individualized around the world. Therefore, the trial permits subjects to continue taking the SoC they were taking prior entering into the trial.

However, SoC may be reimbursed by the Sponsor; handling of reimbursement for such expenses should follow national legislation and/or guidance.

9.9. PRIOR AND CONCOMITANT THERAPIES

9.9.1. Required HP Therapies

Prior to Screening, subjects must be taking doses of the following SoC HP treatments for at least 12 weeks with a minimum of 5 weeks being stable on these doses:

- Calcitriol ≥0.5 µg/day or alfacalcidol ≥1.0 µg/day **and**
- Elemental calcium ≥800 mg/day (e.g., calcium citrate, calcium carbonate, etc.)

Note: The thresholds for calcitriol, alfacalcidol, and calcium are provided above in total daily doses. Acknowledging that the total daily doses may be taken in divided doses throughout the day, the corresponding thresholds would be calcitriol ≥0.25 µg BID; alfacalcidol ≥0.50 µg BID; calcium ≥400 mg BID

Subjects should receive calcium supplementation in the form of calcium citrate in case of concomitant use of proton pump inhibitors or anti-acid therapies.

Subjects may also be on cholecalciferol (vitamin D3) and magnesium supplements as part of their HP treatment or to achieve the recommended daily allowance (RDA), as needed to maintain target ranges of each. The 25 (OH) vitamin D target range is 30-80 ng/mL during treatment phases of the trial. Subjects are to be instructed to take their HP-related supplements at approximately the same time every day throughout the trial. Subjects taking a thiazide diuretic should discontinue at least 4 weeks prior to the baseline Screening 24-hour urine collection scheduled during the week prior to Visit 1.

9.9.2. Prohibited Therapies

The following therapies are prohibited during the blinded phase:

- PTH therapies other than TransCon PTH
- Thiazide or loop diuretics
- Phosphate binders (other than calcium supplements)
- Digoxin, lithium, methotrexate
- Systemic corticosteroids (other than as replacement therapy). Short course use of steroids (≤2 weeks/year) ≤40mg/day is permitted
- Bisphosphonates
- Denosumab
- Biotin >30 µg/day

For the open-label extension period, these medications are allowed only if deemed necessary by the investigator for patient safety considerations. Use of bisphosphonates or denosumab requires consultation with the Medical Monitor to determine potential impact on integrity of relevant endpoints.

TransCon PTH increases calcium, and therefore concomitant use with digoxin (which has a narrow therapeutic index) may predispose patients to digitalis toxicity if hypercalcemia develops.

When TransCon PTH is used concomitantly with digoxin, measure serum calcium and digoxin levels, and monitor for signs and symptoms of digoxin toxicity.

See Section 8.1.2 Exclusion Criteria for prohibited *prior* therapies during the Screening Period.

10. TRIAL PROCEDURES

10.1. TRIAL DURATION

Each subject's participation is expected to last up to approximately 190 weeks including up to approximately 4 weeks of Screening, a 182-week treatment period and a 2 weeks of follow up period after last study drug administration (plus a recommended period of up to approximately 2 weeks between randomization and Visit 1).

10.1.1. Trial Periods and Visits

See Appendix 3 for Schedule of Events.

10.1.2. Screening Period (Week -6 to -2, Day -42 to -14)

The Screening Period will last up to approximately 4 weeks during which clinical data will be collected and Screening procedures will be performed to determine eligibility and optimize subjects on their HP-related supplements prior to enrollment.

Prior to any protocol related activities, Screening procedures, or assignment of a Subject Number, informed consent will be obtained from each potential subject in accordance with GCP and regional regulatory requirements. The format and content of the ICF must be approved by the appropriate institutional review board (IRB)/EC prior to implementation.

The procedures that must be performed and collected during the Screening Period prior to enrollment/randomization are listed within the Schedule of Events (see Appendix 3).

Multiple local laboratory assessments over the approximate 4 weeks of the Screening Period are expected to optimize both the albumin-adjusted or ionized sCa into the normal range, as well as the sMg and vitamin D level. Once the laboratory results are within the optimization ranges and all other entry criteria are met, the subject is eligible to move to the Blinded Treatment Period and be randomized following confirmation by the Medical Monitor or designee. Following randomization, it is recommended to start the treatment period (Visit 1) within 2 weeks from the time of randomization.

The 24-hour urine collection during Screening can be based on a historic 24-hour uCa performed within 52 weeks prior to Screening. Subjects may have been on thiazides, however, subjects must discontinue thiazides at least 4 weeks prior to the baseline 24-hour urine collection scheduled within one week prior to Visit 1.

Investigators are encouraged to provide historical PTH (1-84) values, if available, since HP diagnosis of the subjects.

The Screening Period may be extended with Medical Monitor approval for subjects who fail to optimize to the target laboratory ranges within the Screening window.

Subjects who appear to already be optimized to the target laboratory ranges based on historical laboratory results within 4 weeks prior to Screening and show a 24-hour uCa excretion within

the upper portion of the normal range within 52 weeks of Screening require only a 24-hour urine collection scheduled within 1 week prior to Visit 1.

See Section 11 for further details on procedures and assessments listed in the Schedule of Events.

See Appendix 4 for further details on laboratory assessments to be performed.

Subjects who sign the ICF form but do not meet one or more eligibility criteria (including withdrawing of consent) prior to first study drug dosing will be considered screen failures. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants. Minimal information includes subject ID, demography and reason for screen failure (eligibility criteria or any other reason as applicable).

The decision to rescreen will be made on a case by case basis after discussion with the Medical Monitor, including which Screening procedures may not need to be repeated. Documentation for rescreening must include date and reason for initial exclusion.

10.1.3. Blinded Treatment Period (Visit 1 - 10, Day 1 to Week 26)

Subjects will be randomized in a 3:1 ratio into 2 treatment groups:

- TransCon PTH 18 µg/day*, co-administered with SoC
- Placebo for TransCon PTH (excipient solution) 18 µg/day, co-administered with SoC

* *Dose of TransCon PTH refers to dose of PTH(1-34) administered*

See Appendix 3 for assessments to be performed within the Blinded Treatment Period.

Multiple local laboratory assessments between Visits 2 and 6 may be necessary to guide TransCon PTH/placebo and potentially SoC dose adjustment.

In selected countries, home visits/virtual visits may be performed at Visits 3, 4, 5, 7 and 8 instead of on-site visits. See Section 10.1.7 for further details.

In selected English speaking countries/sites, approximately 2 weeks prior to the final Blinded Treatment Period visit (Visit 10), subjects will be contacted to set up a one-hour phone interview to occur within 2 weeks after the final Blinded Treatment Period visit (Visit 10) to discuss their experience in the trial. In case of subject discontinuation before or at Visit 10, the phone interview will be scheduled to be completed within 2 weeks after the Early Termination Visit. The phone interview will be conducted by an external vendor (see Section 11.9.7).

See Section 11 for further details of procedures and assessments listed in the Schedule of Events.

See Appendix 4 for further details on laboratory assessments to be performed.

10.1.4. Extension Period (Visit 10 - 26 (End of Trial visit), Week 26 to 182)

See Appendix 3 for assessments to be performed within the Extension Period.

See Section 11 for further details of procedures and assessments listed in the Schedule of Events.

See Appendix 4 for further details on laboratory assessments to be performed.

In selected countries, home visits/virtual visits may be performed at Visits 13, 14, 15, 17, 19, 21, 23, and 25 instead of on-site visits. See Section 10.1.7 for further details.

Subjects that show a treatment induced response for either anti-PTH, anti-TransCon or anti-PEG antibodies should be followed 4 to 6 weeks after the treatment ends to determine if antibody levels revert to baseline. Blood samples may be collected every 3 to 6 months, until antibodies can no longer be detected or have a sustained decline.

10.1.5. Unscheduled Visits

Unscheduled visits (UVs) are those visits that occur *at the clinic* between regularly scheduled visits at investigator discretion to assess a potential AE, manage an already documented AE, and/or confirm an abnormal laboratory value requiring Central Laboratory testing. Only focused assessments (guided by the reason for the visit) will occur at these visits. Unscheduled local laboratory visits (ULVs) do not constitute UVs.

10.1.6. Unscheduled Lab Visits

ULVs are those visits that occur *at the local laboratory* between regularly scheduled visits at subject or investigator discretion to assess a potential AE, follow-up on an already documented AE, confirm an abnormal laboratory value requiring Local Laboratory testing. This includes assessment of albumin-adjusted or ionized sCa levels if clinical symptoms of hypo- or hypercalcemia occur at any time during the trial.

10.1.7. Home Visits/Virtual Visits

Home visits/virtual visits may be conducted in place of in-person on-site visits for visits which do not require assessments to be performed on site. Necessary assessments may be performed by a home nurse and the investigational site staff may have a telephone/televideo call with the subject to follow up on general health, AEs, concomitant medications etc. A physical assessment will be performed by the home nurse under the remote supervision of the Investigator.

10.1.8. Early Termination Visits

If a subject discontinue the trial prematurely an Early Termination Visit should be performed, if possible.

If the subject discontinuation occur *prior* to Visit 10, the structure and assessments of the Early termination Visit should be as similar as possible to Visit 10.

If the subject discontinuation occurs *after* Visit 10, the structure and assessments of the Early termination Visit should be as similar as possible to Visit 26.

10.1.9. Follow up Telephone Contact

A telephone contact must take place 2 weeks (+7 days) after last study drug administration to evaluate AEs that were ongoing at the final trial visit and to evaluate the subject for any further AEs during the 2 weeks since last study drug administration.

11. ASSESSMENTS

11.1. MEDICAL HISTORY

Medical history should include any medical condition, signs, symptoms and illnesses ongoing at the time of Informed Consent and must be recorded in the eCRF. The medical history should also capture a detailed description of any prior or ongoing kidney stone, renal insufficiency, cataract, and seizure.

11.2. VITAL SIGN MEASUREMENTS

Subjects should rest for at least 5 minutes before vital sign measurement. The following vital signs should be measured:

- Respiratory Rate
- Body Temperature
- Orthostatic Blood Pressure (BP) & Heart Rate

Assure subjects are well hydrated prior to assessing orthostatic changes.

BP and heart rate are measured while the subject is sitting. The subject is then asked to stand up and, within 2 minutes of doing so, BP and heart rate are measured again.

Orthostasis is defined as a ≥ 20 mmHg decrease in systolic BP, or a ≥10 mmHg decrease in diastolic BP, or an increase in heart rate > 20 bpm after standing. Orthostatic hypotension or orthostatic tachycardia should be captured as an adverse event of special interest (Section 12.1.3 and Section 12.1.4).

11.2.1. Post-Dose Orthostatic Measurements

At Visit 1, a set of orthostatic BP and heart rate should be taken 30 minutes after study drug administration.

At Visit 10, a set of orthostatic BP and heart rate should be taken 30 minutes after TransCon PTH administration for subjects on active vitamin D at Visit 10 or subjects off active vitamin D at Visit 10 and taking study drug ≥ 30 µg/day at the end of the Blinded Treatment Period.

11.3. PHYSICAL EXAMINATION

A complete physical examination should be performed at Screening. Subsequent physical examinations should be performed according to Schedule of Events (see Appendix 3) and may be symptom-directed with the specific components performed at Investigator's discretion. Height and weight will also be measured and recorded at screening.

11.4. PRIOR AND CONCOMITANT MEDICATION

Prior and concomitant therapies include all prescription or over-the-counter medications, vitamins and herbal/nutritional supplements taken within 26 weeks prior to Visit 1 and through the end of the trial, which should be documented with the name of the medication/supplement, dosage information including dose, route, and frequency, dates of administration including start and end dates, and reason for use. Past use of PTH compounds within 5 years will be captured.

11.5. ELECTROCARDIOGRAM

An electrocardiogram (ECG) must be performed and read locally during Screening prior to Visit 1. Standard 12-lead ECG, which includes QT interval and Heart Rate, will be recorded when the subject is in a resting state, prior to blood collection if performed at the same visit.

11.6. X-RAY OF NON-DOMINANT WRIST AND HAND

To confirm epiphyseal closure, an X-ray of the non-dominant wrist and hand must be performed and read locally prior to Visit 1 for subjects 25 years old or younger (as of Screening). A historical X-ray showing epiphyseal closure is acceptable.

11.7. DUAL-ENERGY X-RAY ABSORPTIOMETRY AND TRABECULAR BONE SCORE

To evaluate bone density and quality, a DXA scan of the spine, hip, and forearm, as well as TBS scoring must be performed. TBS scoring will not be performed for subjects 18 to 20 years of age. The DXA images will be read centrally by an external vendor. See the DXA Manual for complete details. The same DXA machine should be used throughout the trial.

A historical DXA performed within 6 months prior to Screening is acceptable for Screening purposes if the same DXA machine will be used throughout the trial and meets the requirements outlined in the DXA Manual. If the historical DXA did not include TBS, TBS analysis should be performed.

11.8. DIETARY CALCIUM QUESTIONNAIRE

Dietary Calcium Questionnaire is a subject-completed assessment of the subject's daily dietary calcium intake. After the questionnaire is completed, site will enter data into the International Osteoporosis Foundation's Dietary Calcium Calculator (https://www.osteoporosis.foundation/educational-hub/topic/calcium-calculator) and print out the calculated results as source documentation to be entered into the electronic data capture (EDC) system by the site staff. Based on the results, site staff will also review and counsel subject to maintain a reasonably stable dietary calcium intake during the trial, potentially optimizing their nutritional calcium intake to get close to the RDA, as well as avoiding unhealthy intake of sodium that can contribute to hypercalciuria.

11.9. CLINICAL OUTCOME ASSESSMENTS

Five subject-completed patient-reported outcome (PRO) measures, and a ClinRO measure will be used in this trial. In countries where the HPES and other measures are available, all participants will be expected to complete the HPES and the other available measures.

Note: All PROs must be completed by the subject without assistance and prior to conducting any clinical assessments.

11.9.1. Hypoparathyroidism Patient Experience Scale

The HPES measures are disease-specific PROs that were developed and validated by the Sponsor to assess relevant patient-reported symptom and disease impacts. The HPES-Symptom assesses the key HP-related physical and cognitive symptoms from the patient perspective. The

HPES-Impact assesses the key impacts of these symptoms on patient functioning and well-being (physical functioning, daily life, psychological well-being, social life and relationships).

The HPES takes approximately 5-10 minutes to complete.

11.9.3. EuroQol 5-dimensional questionnaire

The EuroQol 5-dimensional (EQ-5D) questionnaire is a widely used generic health measure that can be applied to a wide range of health conditions. This measure is used to quantify health related QOL and measures a patient's health across five different domains: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. The measure consists of two components: health state description and evaluation. In the description part, health status is measured in terms of the five dimensions. The respondents rate the level of severity for each dimension using a five-level (EQ-5D-5L) scale. In the evaluation part, the respondents evaluate their overall health status using a EuroQol visual analogue scale (EQ-VAS).

The EQ-5D-5L takes approximately 5 minutes to complete.

11.9.4. 36-Item Short-Form Survey

The 36-Item Short-Form Survey (SF-36) V2 Health Survey (1-week recall) is a multipurpose short-form health survey with 36 questions that yields an eight-scale profile of functional health and general well-being, as well as two psychometrically based physical and mental health summary measures and a preference-based health utility index. It is a practical, reliable and valid measure of physical and mental health. The SF-36 is a generic health survey as it can be used across age (18 and older), disease, and treatment group, as opposed to a disease-specific health survey, which focuses on a particular condition or disease.

The SF-36 can be completed in 5-10 minutes.

11.9.6. Clinical Global Impression of Severity

The Clinical Global Impression of Severity (CGI-S) is a ClinRO measure. It should be completed by the investigator after all clinical assessments are completed. The CGI-S consists of 3 questions that ask the investigator to assess - on a 6-point scale - the subject's overall symptoms, physical symptoms, and cognitive symptoms based on the investigator's clinical judgement, and their impression of the subject's disease from the summary of all assessments and information collected at the visit. The CGI-S provides a clinician's view of the subject's disease status, which is valuable in correlating the subject's self-assessment of their disease status.

The CGI-S takes approximately 1-2 minutes to complete.

11.9.7. Phone Exit Interviews

Phone interviews after the Blinded Treatment Period, in selected English speaking countries/sites are used to assess the subject's experience in the trial in their own words and supply a qualitative view to complement the quantitative clinical outcome assessments (COAs). The exit interviews will collect information on subject's evaluation of treatment received, and the subject's experience of taking part in the clinical trial, and aid in the interpretation of changes in clinical and PRO scores, including the HPES-Symptom and HPES-Impact measures, to determine what constitutes meaningful change for patients with HP.

11.10. LOCAL TOLERABILITY ASSESSMENT

Local Tolerability is assessed based on the presence of an injection site reaction (ISRs) captured as an AE (see section 12.4.3.4 for ISR reporting).

At Visit 1, assessment of local tolerability including redness, itching and swelling is performed by trial staff at the time of the first study drug injection and at least 15 minutes post-dose.

At Visit 10, the first dose of open-label TransCon PTH is administered on-site only for subjects still taking active vitamin D or subjects off active vitamin D and taking study drug dose ≥30 µg/day at the end of Blinded Treatment Period. An assessment of local tolerability including redness, itching and swelling is performed by trial staff using the Local Tolerability Scale at the time of the TransCon PTH injection and at least 15 minutes post-dose.

As part of the local tolerability assessment at Visit 1 and 10, the subject will complete the Wong-Baker FACES® Pain Rating Scale to assess the pain at the injection site that the subject is experiencing after the injection.

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11.12. SUBJECT DIARY

Subjects are trained on the diary during Screening and the diary should be reviewed at the visit by trial staff as part of study drug compliance and SoC/PRN medication doses review.

An eDiary solution will be used with subject's own device or with a provision device.

Subjects will be required to complete a daily diary until Visit 13 to capture the following:

- Study drug, starting at Visit 1 (administration date and time, dose, location of injection site)
- SoC (administration date, name and dose), including PRN medication doses

Subjects will be required to complete a weekly diary starting from Visit 13 to Visit 18 to capture TransCon PTH administration and any SoC/PRN medication doses.

Paper diary might be used as back-up solution.

Diary completion during the Screening Period assists in tracking SoC optimization. The minimum 7 days between the Screening Period and Visit 1 should be used as an opportunity for subjects who are already optimized on HP-related supplements prior to Screening to become acquainted with the diary prior to enrollment/randomization.

11.13. ADVERSE EVENT ASSESSMENTS

At each visit, the subject should be asked about the following to assess for any potential AEs:

- General well-being
- Any changes to health or medications since the previous visit
- Hypo- or hypercalcemic symptoms since the previous visit
- Vasodilatory symptoms as adverse events of special interest (AESI)
- Emergency/urgent care visits or hospitalizations since the previous visit

Additionally, the site staff will review subject diary data to determine if diary entries reflect any AEs with a reference to the AE section and at applicable visits, changes from baseline noted during a physical examination should be assessed for potential AEs.

At the investigator's discretion, additional assessments, including an examination of injection sites, a physical examination, or additional laboratory assessment, may be performed even if not required at the specific trial visit or if an UV or ULV must be scheduled.

See Section 12.3 for details on reporting AEs.

11.14. LABORATORY ASSESSMENTS

Samples will be obtained at a minimum for both central and local laboratory tests to be performed as outlined in Appendix 4.

Note:

- **Blood collection must occur prior to on-site study drug administration, when applicable**
- **On the day of lab assessments, subjects should avoid exercise prior to blood collection**
- **On the day of lab assessments, subjects should be instructed to take their SoC (as applicable) and eat their usual breakfast prior to blood collection**

Investigators must be able to receive local laboratory results within a time frame sufficent to allow instructions to subjects on dose adjustments preferably within 48 hours of blood collection.

All local laboratory results required by this protocol will be entered into the EDC system by the site staff.

Data from samples obtained for analysis of antibodies against PTH, TransCon PTH and PEG will be used to support evaluation of post-dose antibody detection. Blood samples may be used for additional exploratory characterization of anti-drug antibody responses.

Subjects that show a treatment induced response for either anti-PTH, anti-TransCon or anti-PEG antibodies should be followed 4 to 6 weeks after the treatment ends to determine if antibody levels revert to baseline. Blood samples may be collected every 3 to 6 months, until antibodies can no longer be detected or have a sustained decline.

If a subject experience a suspected anaphylactic reaction (excluding anaphylactic reactions due to confirmed exposure to an allergen known to be a trigger for an individual subject), blood should be drawn as soon as possible (ideally within 48 hours) for tryptase and total IgE. The subject should also be further evaluated (by the investigator and/or an allergist or similar specialist) to confirm/refute an anaphylactic reaction through a thorough history, with consideration given to interval testing of tryptase, total IgE, and a re-challenge with study drug.

Samples for measuring Free PTH will be collected in a subset of subjects at selected sites. The aim is to obtain samples from as many subjects as possible but expect a minimum of approximately 30% of the subjects.

11.15. LIFESTYLE MODIFICATION

11.15.1. Dietary Modifications

Subjects should be advised to consume approximately the same amount of calcium from their diet every day to minimize the effect of dietary calcium on fluctuation in sCa level. The Investigator or site staff will counsel the subjects about their dietary calcium intake based on the dietary calcium questionnaire and counseled to avoid excessive sodium intake.

11.15.2. Exercise Modifications

Subjects should be advised to avoid exercise prior to visits which include blood collection.

11.15.3. Contraception

TransCon PTH did not induce adverse effects on male or female fertility in dedicated fertility studies conducted in rats. Further, TransCon PTH did not induce adverse effects on embryofetal developmental in pregnant rats and rabbits (see Investigator's Brochure *Section 4.4.4 – Reproductive Performance and Developmental Toxicity Studies*).

Irrespectively, acceptable highly effective contraception during the trial and for 2 weeks after the last dose of study drug is required for women of childbearing potential if sexually active, and pregnancy testing for women of childbearing potential will be performed throughout the trial.

See Appendix 1 for further guidance on acceptable highly effective contraception.

See Appendix 4 for further details on pregnancy testing schedule.

11.15.4. Study Drug Administration

11.15.4.1. Blinded Treatment Period Administration

The first dose of study drug will be administered by the subject in the clinic, and the subject will be observed for at least 30 minutes for local tolerability assessment and adverse reactions, including orthostatic hypotension and orthostatic tachycardia. Subjects will inject subsequent doses of study drug daily at home.

It is recommended that subjects inject the study drug every day in the evenings before bedtime (starting at day 2).

11.15.4.2. Extension Period Administration

For the subjects still on active vitamin D at Visit 10 or the subjects off active vitamin D at Visit 10 and taking TransCon PTH/placebo dose ≥30 µg/day at the end of Blinded Treatment Period, the first dose of open-label TransCon PTH is administered by the subject in the clinic, and the subjects will be observed for at least 30 minutes for local tolerability assessment and adverse reactions, including orthostatic hypotension and orthostatic tachycardia.

The subjects should get back to the evening dosing as before the day after Visit 10.

11.15.5. Hypo- or Hypercalcemia Symptom Management

Most HP subjects are able to recognize their symptoms of hypocalcemia, and many can recognize symptoms of hypercalcemia. Just as in normal management of patients with HP, if hypo- or hypercalcemic symptoms develop any time in between trial visits, subjects should contact the site and visit the local laboratory (i.e., ULV) to assess albumin-adjusted or ionized sCa. Additionally, as in normal management of patients with HP, all subjects will be permitted to take extra active vitamin D and/or calcium supplements as PRN medications to resolve symptoms of hypocalcemia, and reduce calcium and/or active vitamin D supplements (or hold/reduce their dose of Transcon PTH if off SoC) to resolve acute symptoms of hypercalcemia. Subjects should be encouraged to visit the local laboratory for assessment of sCa and albumin, or ionized calcium levels for symptoms of hypercalcemia.

12. ADVERSE EVENT ASSESSMENT AND REPORTING

12.1. DEFINITION

12.1.1. Adverse Event

An AE is defined as any untoward medical occurrence in a clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with the treatment. An Adverse event can therefore be any of the following:

- Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational medicinal product (IMP) or other protocol-imposed intervention, regardless of attribution.
- AEs not previously observed in the subject that emerge during the protocol-specified AE reporting period, including signs or symptoms associated with hypoparathyroidism that were not present prior to the AE reporting period.

- Complications that occur as a result of protocol-mandated interventions (e.g., invasive procedures such as cardiac catheterizations).
- If applicable, AEs that occur prior to assignment of study treatment associated with medication washout, no treatment run-in, or other protocol-mandated intervention.
- Preexisting medical conditions (other than the condition being studied) judged by the investigator to have worsened in severity or frequency or changed in character during the protocol-specified AE reporting period.

12.1.2. Serious Adverse Events

An SAE is any untoward medical occurrence at any dose that meets any of the following criteria:

- It results in death (i.e. the AE cause or leads to death).
- It is life threatening (i.e. the AE, in the view of the investigator, places the subject at immediate risk of death. It does not include an AE that, had it occurred in a more severe form or was allowed to continue, might have caused death).
- It requires or prolongs inpatient hospitalization (see Section 12.4.3.6).
- It results in persistent or significant disability/incapacity (i.e., the AE results in substantial disruption of the subject's ability to conduct normal life functions).
- It results in a congenital anomaly/birth defect in a neonate/infant born to a mother exposed to the study drug.
- It is considered a significant medical event by the investigator based on medical judgment (e.g., may jeopardize the subject or may require medical/surgical intervention to prevent one of the outcomes listed above).

The terms "severe" and "serious" are not synonymous. Severity refers to the intensity of an AE (e.g., rated as mild, moderate, or severe; see Section 12.3.1; the event itself may be of relatively minor medical significance (such as severe headache without any further findings.

Severity and seriousness need to be independently assessed for each AE recorded on the eCRF.

Serious AEs are required to be reported by the investigator to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 12.5.2 for reporting instructions).

12.1.3. Adverse Events of Special Interest (AESIs)

AESIs are a subset of Events to Monitor (EtMs) of scientific and potential medical concern specific to the product, for which ongoing monitoring and reported by the Investigator within 24 hours to the Sponsor is required. Such an event might require further investigation in order to characterize and understand it. Depending on the nature of the event, rapid communication by the trial Sponsor to other parties (e.g. Regulatory Authorities) may also be warranted.

12.1.4. TransCon PTH Adverse Events of Special Interest

AEs of special interest for this study include the following:

- Vasodilatory signs and symptoms which may include orthostatic dizziness, lightheadedness, weakness, blurring of vision, pre-syncope, syncope, headache, orthostatic hypotension,

orthostatic tachycardia/palpitations. Such symptoms are usually transient in nature and can be managed by dosing at bedtime, while reclining. PTH is known to have vasodilatory effects (Rambausek 1982)

- Persistent severe hypocalcemia (as defined in Section 9.6.1)
- Persistent severe hypercalcemia (as defined in Section 9.6.1)

12.1.5. Special Situation

Special situations are non-standard medical conditions that provide valuable information (e.g. clinical, safety) about a medicinal product, even when they do not occur in association with an AE or medical condition. Examples of special situations include and should all be captured in the eCRF:

- Pregnancy
- Breastfeeding
- Overdose
- Drug abuse
- Misuse
- Occupational exposure
- Lack of therapeutic efficacy
- Medication error

The Medical Monitor will review all safety information on an ongoing basis.

12.2. METHODS AND TIMING FOR ASSESSING AND RECORDING SAFETY VARIABLES

The investigator is responsible for ensuring that all AEs, AESIs and SAEs that are observed or reported during the study are collected and reported to Ascendis Pharma, in accordance with FDA CFR 312.32 (IND Safety Reports) and ICH E6.

12.3. ADVERSE EVENT REPORTING PERIOD

The Adverse Event Reporting Period is the period requiring reporting of AEs, AESIs and SAEs for any subjects exposed to IMP product and or any study related procedures. Reporting period begins from the time when the informed consent is obtained and ends 2 weeks following the last administration of study treatment or study discontinuation/termination, whichever is earlier. After this period, investigators should only report SAEs that are attributed to prior study treatment Severity, Causality, and Outcome Assessment.

12.3.1. Assessment of Severity of Adverse Events

The World Health Organization (WHO) toxicity grading scale will be used for assessing AE severity. Table 2 will be used for assessing severity for AEs that are not specifically listed in the WHO toxicity grading scale.

Table 2: Adverse Event Severity Grading Scale for Events Not Specifically Listed in WHO Toxicity Grading Scale

Grade	Severity
1	Mild; transient or mild discomfort (< 48 hours); no medical intervention or therapy required
2	Moderate; mild to moderate limitation in activity; some assistance may be needed; no or minimal medical intervention or therapy required
3	Severe; marked limitation in activity; some assistance usually required; medical intervention or therapy required; hospitalization possible
4	Life-threatening; extreme limitation in activity; significant assistance required; significant medical intervention or therapy required, hospitalization or hospice care probable

Regardless of severity, some events may also meet seriousness criteria. Refer to definition of a serious AE (see Section 12.1.2).

12.3.1.1. Causality Rating

All AEs, AESIs and SAEs whether volunteered by the subject, discovered by study personnel during questioning, or detected through physical examination, laboratory test, or other means must be reported appropriately.

Each reported AE, AESIs or SAE must be described by its duration (i.e., start and end dates), seriousness criteria if applicable, suspected relationship to the TransCon PTH (see following guidance), and actions taken. To ensure consistency of AE and SAE causality assessments, investigators should apply the following general guideline:

Related (Yes) – There is a plausible temporal relationship between the onset of the AE and administration of TransCon PTH. The AE cannot be readily explained by the subject's clinical state, intercurrent illness, or concomitant therapies. The AE follows a known pattern of response to TransCon PTH or with similar treatments. And/or the AE abates or resolves upon discontinuation of TransCon PTH or dose reduction and, if applicable, reappears upon re-challenge.

Not Related (No) – Evidence exists that the AE has an etiology other than the TransCon PTH (e.g., preexisting medical condition, underlying disease, intercurrent illness, or concomitant medication). The AE has no plausible temporal relationship to TransCon PTH administration (e.g., cancer diagnosed 2 days after first dose of study drug).

Expected AEs are those AEs that are listed or characterized in the current Investigator's Brochure.

Unexpected AEs are those not listed in the current IB or not identified. This includes AEs for which the specificity or severity is not consistent with the description in the Investigator's Brochure.

12.3.1.2. Outcome Assessment

Subjects will be followed until AEs have either resolved, subjects have returned to their baseline status, or subjects are deemed stable or commensurate with ongoing disease processes. One of five outcomes listed below must be recorded:

Recovered/Resolved – The event has stopped. The stop date of the event must be recorded.

Recovering/Resolving – The subject is clearly recovering from an event. The event is not yet completely resolved.

Not Recovered/Not Resolved – The event is still ongoing. (Could include stable and commensurate with ongoing disease processes).

Recovered/Resolved with sequelae – The event has reached a state where no further changes are expected, and the residual symptoms are assumed to persist. An example is hemiparesis after stroke.

The stop date of the event must be recorded. In case of SAE, the sequelae should be specified.

Fatal – The subject has died as a consequent of the event. Date of death is recorded as stop date for the AE.

Unknown – Unknown to investigator, e.g. subject lost to follow up.

12.4. PROCEDURES FOR ELICITING, RECORDING AND REPORTING ADVERSE EVENTS

12.4.1. Eliciting Adverse Events

A consistent methodology for eliciting AEs at all subject evaluation time points should be adopted. Examples of non-directive questions include:

- "How have you felt since your last clinical visit?"
- "Have you had any new or changed health problems since you were last here?"

12.4.2. Recording Procedures for All Adverse Events

All AEs will be documented in response to question about the subject's well-being and whether any possible changes in well-being have occurred since the previous visit.

AEs, including AESIs and SAEs, will be documented through the end of the subject's participation in the trial or Early Termination Visit. All AEs must be recorded on the appropriate eCRF. AEs either observed by the investigator or reported by the subject must be recorded regardless of causality. The following attributes must be documented for each reported AE:

- Subject ID
- Description
- Onset date (if AE was present on Day 1, include whether onset was prior to or after the first dose of the study drug)
- Resolution date, if applicable
- Severity
- Causality (relationship to the study drug)
- Outcome

- Action taken
- Determination of "seriousness criteria" (whether serious or not serious)

Any medical history condition, signs, symptoms, and illnesses active during the Screening Period will be captured as baseline (preexisting) events, if appropriate, to assure that any change(s) in these experiences during the trial also are recorded as an AE and a complete safety profile is obtained. An event that occurs after signing of ICF but prior to the first study drug administration will be documented as medical history unless the event is trial procedure–related, in which case it will be reported as a non–treatment-emergent AE. Any new or worsening pretreatment event that occurs from the time of the first study drug administration until the EOT Visit will be recorded as an AE.

Routine titration of chronic, concomitant medications will not be considered to meet the criteria for AEs.

Investigators should use correct medical terminology/concepts when reporting AEs, AESIs or SAEs. Avoid colloquialisms and abbreviation (e.g., hypertension for elevated BP that persists and requires chronic treatment and follow-up, or increased blood pressure for elevated blood pressure that occurs for a limited time and does not persist or require ongoing treatment).

AEs will be documented at the maximum intensity experienced. If a previously recorded and closed AE or condition recorded as part of medical history increases in severity or frequency, it will be recorded as a new AE.

An accidental overdose is not an AE if there are no signs or symptoms. Any undesirable medical occurrence resulting from an accidental overdose is an AE and should be recorded and reported on the appropriate eCRF. Regardless of classification as an AE or not, *all* overdoses should be documented, and the subject(s) monitored. Since accidental overdoses with the study drug could have serious clinical consequences and/or represent a compliance issue, they should be reported to the Medical Monitor immediately and evaluated by the Sponsor.

12.4.3. Specific Instructions for Recording Adverse Events

12.4.3.1. Abnormal Laboratory Values

Not every laboratory abnormality qualifies as an AE. A laboratory test result must be reported as an AE if it meets any of the following criteria:

- Is accompanied by clinical symptoms
- Results in a change in study treatment (e.g., dosage modification or titration, treatment interruption, or treatment discontinuation). Abnormal serum calcium values will not be considered AEs unless associated with a sign or symptom*
- Results in a medical intervention (e.g., potassium supplementation for hypokalemia) or a change in concomitant therapy
- Is clinically significant in the investigator's judgment

It is the investigator's responsibility to review all laboratory findings. Medical and scientific judgment should be exercised in deciding whether an isolated laboratory abnormality should be classified as an AE.

Observations of the same clinically significant laboratory abnormality from visit to visit should only be recorded once on the Adverse Event eCRF.

** Abnormal serum calcium values - whether or not associated with titration of study drug, calcium, or active vitamin D doses - will not be considered AEs unless associated with a sign or symptom. Serum calcium is a pharmacodynamic marker of study drug therapy and thus used to guide titration of study drug, calcium, and active vitamin D doses (per Appendix 2).*

12.4.3.2. Abnormal Vital Sign Values

Not every vital sign abnormality qualifies as an AE. A vital sign result must be reported as an AE if it meets any of the following criteria:

- Is accompanied by clinical symptoms
- Results in a change in study treatment (e.g., dosage modification, treatment interruption, or treatment discontinuation)
- Results in a medical intervention or a change in concomitant therapy
- Is clinically significant in the investigator's judgment

It is the investigator's responsibility to review all vital sign findings. Medical and scientific judgment should be exercised in deciding whether an isolated vital sign abnormality should be classified as an AE.

If a clinically significant vital sign abnormality is a sign of a disease or syndrome (e.g., high blood pressure), only the diagnosis (i.e., hypertension) should be recorded on the Adverse Event eCRF.

Observations of the same clinically significant vital sign abnormality from visit to visit should only be recorded once on the Adverse Event eCRF.

12.4.3.3. Diagnosis vs. Signs and Symptoms

If known at the time of reporting, a diagnosis should be reported rather than individual signs and symptoms (e.g. record only heart failure rather than dyspnea, orthopnea and extremity edema). However, if a constellation of signs and/or symptoms cannot be medically characterized as a single diagnosis or syndrome at the time of reporting, it is acceptable to report the information that is currently available as separate AEs. If a diagnosis is subsequently established, it should be reported as follow-up information.

12.4.3.4. Injection Site Reactions

ISRs that occur during or after study drug administration and that are judged to be related to study drug injection are deemed to be AEs. These AEs should be captured as a unified diagnosis on the AE eCRF (e.g. as an “injection site reaction” rather than capturing “injection site bleeding” and “injection site induration” as separate adverse events). The diagnosis is at the discretion of the investigator. Signs, symptoms, and features of the injection site reaction should be recorded on a dedicated corresponding eCRF.

12.4.3.5. Deaths

All deaths that occur during the protocol-specified AE reporting period, regardless of attribution, will be reported to the appropriate parties. When recording a death, the event or condition that caused or contributed to the fatal outcome should be reported as the single medical concept. If the cause of death is unknown and cannot be ascertained at the time of reporting, report "Unexplained Death".

12.4.3.6. Hospitalizations for Medical or Surgical Procedures

Any AE that results in hospitalization or prolonged hospitalization should be documented and reported as an SAE. If a subject is hospitalized to undergo a medical or surgical procedure as a result of an AE, the event responsible for the procedure, not the procedure itself, should be reported as the SAE. For example, if a subject is hospitalized to undergo coronary bypass surgery, record the heart condition that necessitated the bypass as the SAE. Hospitalizations for the following reasons do not require reporting:

- Hospitalization or prolonged hospitalization for diagnostic or elective surgical procedures for preexisting conditions
- Hospitalization or prolonged hospitalization required to allow efficacy measurement for the study or
- Hospitalization or prolonged hospitalization for scheduled therapy of the target disease of the study

12.4.3.7. Preexisting Medical Conditions

A preexisting medical condition is one that is present at the start of the study. Such conditions should be reported as medical and surgical history. A preexisting medical condition should be re-assessed throughout the trial and reported as an AE or SAE only if the frequency, severity, or character of the condition worsens during the study. When reporting such events, it is important to convey the concept that the preexisting condition has changed by including applicable descriptors (e.g., "more frequent headaches").

12.4.3.8. Pregnancy

If a female subject becomes pregnant while receiving the study drug or within two weeks after the last dose of study drug, or if the female partner of a male study subject becomes pregnant while the study subject is receiving the study drug or within two weeks, a Pregnancy report should be completed and expeditiously submitted to Ascendis Pharma. Follow-up to obtain the outcome of the pregnancy should also occur and the outcome reported to Ascendis Pharma. Abortion, whether accidental, therapeutic, or spontaneous, should always be classified as serious, and expeditiously reported as an SAE. Similarly, any congenital anomaly/birth defect in a child born to a female subject exposed to the study drug should be expeditiously reported as an SAE.

12.4.3.9. Product Complaints

A Product Complaint is defined as any written or oral information received from a complainant that alleges deficiencies related to identity, quality, safety, strength, purity, reliability, durability,

effectiveness, or performance of a product after it has been released and distributed to the commercial market or clinical trial.

In this study, the TransCon PTH delivery system consists of a multi-use cartridge integrated into a device to constitute a pre-filled injection pen which is considered a medical device. The investigator must report all medical device complaints to the Sponsor. The investigator should document as much information as possible including the product batch number and forward the information to the Sponsor immediately (refer to the pharmacy manual for further details). If the medical device results in an adverse event to the study patient, the event must be reported on the AE eCRF and submitted through the EDC system. If the event is serious, the AE eCRF must be completed immediately (i.e., no more than 24 hours after learning of the event), as outlined in Section 12.5.2.

12.5. SAFETY REPORTING REQUIREMENTS

12.5.1. Non-Serious Adverse Events Leading to Discontinuation

If situation permits, non-serious events (including laboratory abnormalities and pregnancies) that may require permanent discontinuation of study drug should be discussed with the Medical Monitor prior to making any final decision.

12.5.2. Reporting

All initial and follow-up information regarding SAEs, AESIs, and Special Situations reporting must be reported by the investigator to the Sponsor or its representatives within 24 hours of discovery/awareness, including those related to protocol-mandated procedures and regardless of suspected causality.

For each AE recorded on the AE eCRF, the investigator will make an assessment of seriousness (see Section 12.1.2 for seriousness criteria), severity (Section 12.3.1), and causality (see Section 12.3.1.1).

Reporting must not be delayed by waiting for additional information. The minimum information required for reporting an SAE, AESIs, and Special Situations are the AE term (diagnosis), patient, study drug, reporter, and the investigator's initial causality assessment. Additional information must be reported to the Sponsor or its representatives as a follow-up report. All SAEs, AESIs, and Special Situations (including follow-up information) must be reported using the Safety report form or the Pregnancy report form provided. A completed Safety report form / Pregnancy report form must be uploaded to the Safety Reporting Portal at:

Safety.ascendispharma.com

Specific instructions regarding completion of the form and reporting details are provided on the Safety report form.

SAEs, AESIs, and Special Situations information is collected and reported via SAE Forms provided by the Sponsor or its representative. Pregnancy information is collected and reported via Pregnancy Forms provided by the Sponsor or its representative. The Sponsor (or its representatives) is responsible for reporting within the time frame required by applicable regulations all SAEs qualifying as SUSARs to:

- Investigators.
- Central IRBs/HRECs/IECs (if applicable).
- National ethics committees (if applicable).
- Appropriate regulatory authorities.

It is the investigators' responsibility to comply with the requirements of their local IRB/HREC/IEC for reporting SUSARs, other SAEs, and any new and/or relevant safety information provided by the Sponsor or its representatives. At minimum, SUSARs must be brought to the attention of these review boards in accordance with regional regulations.

13. SAFETY MONITORING

The Sponsor will conduct an ongoing review of all trial data, with particular attention given to laboratory findings (in particular related to albumin adjusted serum calcium, ionized calcium), AEs, and concomitant medications. Any important safety trends or other findings considered related to the study drug will be reported to the investigators and to regulatory authorities. In particular, the Sponsor will notify investigators and regulatory authorities of AEs that:

- Fulfill the criteria for SUSARs.
- Occur at a meaningfully greater frequency than described in the current Investigator's Brochure *Section 6.8 – Reference Safety Information for Assessment of Expectedness of Serious Adverse Reactions*.

Any AE that occurs during the clinical trial must be monitored and followed up until:

- It has resolved or receded
- Pathology laboratory findings have returned to normal
- Steady-state has been achieved
- It has been shown to be unrelated to the study drug and/or trial related procedure

Details will be described in the Safety Management Plan.

14. DEVICE ASSOCIATED HAZARDS, RISKS, AND ADVERSE EVENTS

During the device development process, risk management activities have been performed according to ISO 14971. Risk analyses have been performed using Failure Mode and Effects Analysis techniques to address risks related to design, use and manufacturing of the TransCon PTH prefilled pen. The severity of hazards related to risks has been assessed and used to ensure appropriate risk mitigation and evaluation of residual risks. The severity rating applied throughout the TransCon PTH prefilled pen risk management activities are listed in Table 3.

An analysis of risks associated with the use of the TransCon PTH prefilled pen has been performed. This analysis addressed 73 use related risks. All these risks have been mitigated or reduced to an acceptable level by packaging design or by labeling (IFU). The use related risk analysis of the TransCon PTH prefilled pen identifies three residual risks related to a potential hazard with a severity rating of S4 or above. These three risks relate to swallowing of small parts (choking hazard), cross contamination between multiple users and infections. These are class-related risks related to the single use needle or to the single patient use prefilled pen. These

risks are common for marketed prefilled pen combination products and are therefore evaluated to be acceptable. The TransCon PTH prefilled pens are delivered with Ypsomed Clickfine AutoProtect single use needles designed to reduce the potential risk associated with accidental needle stick injuries. The remaining 70 use-related risks, including risks related to under-dosing, over-dosing or injection of a degraded drug product, relate to hazards rated S3 or lower. The packaging and IFU have been developed and tested through a series of formative usability studies (one platform prefilled pen study and six TransCon PTH prefilled pen studies). In conclusion the usability testing of the TransCon PTH prefilled pen, packaging and IFU supported the effectiveness of the risk mitigations as well as the safe and effective use for both untrained and trained intended users. Finally, it is noted, that the risk analysis did not identify a need for cleaning of the device during its use period. The risk evaluation including the assessment of the residual risks concludes that the use of the TransCon PTH prefilled pen is safe and effective.

The Phase 2 trial (TransCon PTH TCP-201) has been conducted using the TransCon PTH prefilled pen configurations that are also intended to be used in the Phase 3 trial (TCP-304). No AEs relating to the device constituent of the TransCon PTH prefilled pen has been reported. Less than ten complaints relating to the device constituent, IFU and needles have been registered during the clinical trial. One complaint has led to a minor update of the IFU and the rest have not triggered any changes.

Table 3: Severity Ratings Applied in Risk Evaluation

Severity Rating				
Negligible (S1)	**Minor (S2)**	**Serious (S3)**	**Critical (S4)**	**Catastrophic (S5)**
Inconvenience or momentary discomfort	Temporary injury or impairment without requiring professional medical attention Temporary loss of efficacy	Injury or impairment probably requiring professional medical treatment Long term loss of efficacy	Permanent impairment or life-threatening injury	Death

15. STATISTICS

15.1. GENERAL

Details of applicable statistical methods will be provided in a statistical analysis plan (SAP) which will be finalized before trial unblinding and database lock of the Blinded Treatment Period. If discrepancies exist between the text of the statistical analysis as planned in the protocol and the final SAP, the final SAP will define the planned analysis of record.

All statistical tests will be two-sided and tested at the statistically significant level of 0.05. Confidence intervals will be 2-sided 95% confidence intervals, unless stated otherwise.

15.2. ENDPOINTS

15.2.1. Efficacy Endpoints

15.2.1.1. Primary Efficacy Endpoint

At 26 weeks of treatment, the proportion of subjects with:

- Albumin-adjusted sCa measured within 4 weeks prior to and on Week 26 visit are within the normal ranges (8.3-10.6mg/dL)*; and
- Independence from active vitamin D** and
- Independence from therapeutic doses of calcium (i.e., taking calcium supplements ≤600 mg/day). This dose of calcium ≤600 mg/day in the form of tablets, powder, liquid suspension, or transdermal patch is considered as "supplemental" to meeting recommended daily intake for general health, as opposed to a "therapeutic" dose to treat hypoparathyroidism*** and
- No increase in prescribed study drug within 4 weeks prior to Week 26 visit****

* Except for at the Week 26 visit, confirmation that an albumin-adjusted sCa is "abnormal" requires 2 consecutive results outside the normal range within 4 weeks prior to the Week 26 visit.

** *Independence* from active vitamin D will be defined as a daily standing dose equal to zero on all days AND use of any PRN vitamin D ≤7 days within 4 weeks prior to the Week 26 visit.

*** *Independence* from therapeutic calcium will be defined as average daily standing dose ≤600 mg AND use of PRN doses on ≤7 days within 4 weeks prior to the Week 26 visit.

**** Dose *decrease* permitted for safety reasons.

15.2.1.2. Secondary Efficacy Endpoints

15.2.1.2.1. Key Secondary Efficacy Endpoints

Change from baseline at 26 weeks of treatment:

- HPES Symptom – Physical domain score
- HPES Symptom – Cognitive domain score
- HPES Impact - Physical functioning domain score
- HPES Impact – Daily life domain score
- 36-Item Short Form Survey (SF-36) Physical functioning subscale score

15.2.1.2.2. Other Secondary Efficacy Endpoints

The key secondary efficacy endpoints and the following efficacy endpoint will be evaluated at predefined timepoints during the Extension Period.

- The proportion of subjects that meet the following criteria:
  - Albumin-adjusted sCa measured within the normal range (8.3-10.6 mg/dL); and

- Independence from active vitamin D (i.e., standing dose of active vitamin D equal to zero on the day prior to the Week 52 visit or other visits of interest); and
- Independence from therapeutic doses of calcium (i.e., standing dose of elemental calcium ≤ 600 mg on the day prior to the Week 52 visit or other visits of interest).

The following endpoints will be evaluated at predefined timepoints during the Blinded Treatment and the Extension Period:

- Calcium and active vitamin D doses
- Daily "pill burden" of active vitamin D and calcium (as oral tablets, powder, liquid solutions, liquid suspensions, or transdermal patches)
- sP
- Albumin-adjusted sCa x sP product, including proportion of subjects with albumin-adjusted sCa x sP product ≤55 mg^2/dL^2, ≤52 mg^2/dL^2, and ≤44 mg^2/dL^2
- Albumin-adjusted sCa
- BMD and TBS by DXA
- Bone turnover markers (serum P1NP and CTx)
- sMg
- EuroQol 5-Dimensional Questionnaire (EQ-5D)
- Clinical Global Impression of Severity (CGI-S)
- HPES: HPES Impact domain scores (Psychological Well-being and Social life and Relationships) and HPES Symptom and Impact total scores
- SF-36: SF-36 subscale scores (Role Limitations due to Physical Health Problems, Bodily Pain, General Health, Vitality, Social Functioning, Role Limitations due to Emotional Problems, and Mental Health) and SF-36 component scores (Physical component score and Mental component score)

15.2.2. Safety Endpoints

The following safety endpoints will be assessed during the Blinded Treatment and Extension Periods:

- Incidence of AEs, AESI and SAEs
- Serum chemistry, hematology, and
- 24-hour urine chemistry (including urine calcium and urine creatinine clearance) at prespecified timepoints including at Week 26
- Clinical events of hypo- or hypercalcemia (emergency/urgent care visits and hospitalizations)
- Injection site tolerability (based on AEs)
- Evaluation of anti-PTH, anti-TransCon PTH and anti-PEG antibody responses
- Vital signs

15.2.3. Exploratory Endpoints

CCI

[redacted]

15.3. STATISTICAL ANALYSIS

The Intent-To-Treat (ITT) Population consists of all subjects who were randomized and received at least one dose of blinded study drug. All efficacy analysis will be based on ITT and treatment assignment per randomization. The Safety Analysis Population consists of all randomized subjects who received at least one dose of study drug. The safety analyses will be based on the Safety Analysis Population and actual treatment received.

In general, descriptive statistics summary will be generated by double blind and extension phases.

Categorical data will be presented using counts and percentages of subjects. Continuous variables will be presented using number of subjects, mean, standard deviation (SD)/standard error (SE), median, minimum and maximum.

Efficacy Analysis

The primary estimand for the primary analysis is defined by the following components:

- Population: Refer to Section 8 Trial Population, with inclusion/exclusion criteria considered. The efficacy analyses will be based on the ITT Population
- Efficacy Endpoints: Refer to Section 15.2.1.1
- Handling missing data (intercurrent events): Subjects may have missing data for primary endpoint assessments due to early discontinuation from study drug, missing lab visits, non-evaluable lab values, etc. Such subjects will be included in primary analysis. Subjects with no Week 26 albumin-adjusted sCa OR with >25% (i.e., >7 days) missing diary data of active vitamin D or calcium during the 4 weeks will be considered as non-responders.
- Analysis: CMH test stratified by etiology of hypoparathyroidism (post-surgical vs. other) is the primary analysis method and will be used to compare the proportion of subjects meeting the listed criteria of the primary endpoint (responders vs. non-responders) in the TransCon PTH vs. placebo groups
- Population-level summary: Number and percentage of subjects meeting the primary endpoint criteria defined in Section 15.2.1.1 will be provided.

Sequential testing will be applied to control the family-wise type-1 error rate for the primary and key secondary endpoints. Details will be specified in the SAP.

In general, continuous endpoints during Blinded Treatment Period will be analyzed using ANCOVA model with unequal covariance. The model will include the change from baseline for

the endpoint of interest as a response variable, treatment assignment and etiology of hypoparathyroidism as fixed factor and baseline value of the endpoint will be entered as a covariate, unless otherwise specified in the SAP. The key secondary PRO efficacy endpoints will be analyzed as continuous and in terms of change from baseline using the described ANCOVA model with multiple imputation for missing post-baseline assessments.

Categorical endpoints during Blinded Treatment Period will be analyzed using CMH test stratified by etiology of hypoparathyroidism.

All efficacy endpoints will be summarized descriptively in Extension Period analysis.

Pharmacokinetic Analysis

The PK parameters and their statistical evaluation will be included in the Clinical Study Report. PK data will be used to describe plasma concentration at steady-state. Potential impact of any anti-PTH, anti-TransCon PTH and anti-PEG antibodies detected will be included in the evaluation. The Free PTH results will additionally be added to the population PK analysis.

Safety Analysis

The reporting of the safety data is descriptive. Descriptive analysis will include the incidence TEAEs, and changes in laboratory, vital signs, and pre-existing and treatment induced, anti-PTH, anti-TransCon PTH and anti-PEG antibodies responses. Listings of all safety endpoints by treatment group will be presented.

Interim Analysis

The analysis of the Blinded Treatment Period will be conducted after database lock of the Blinded Treatment Period, which will occur prior to database lock of the Extension Period. No interim analysis is planned.

15.4. POWER CALCULATION

The sample size is determined based on considerations from both statistical power and adequate safety exposure perspectives. Assuming that the response rate is 70% for TransCon PTH and 15% for placebo for the primary endpoint at 26 weeks, 68 subjects randomized 3:1 to active TransCon PTH vs. placebo will have approximate statistical powers of 99% at alpha = 0.05, and 95% at alpha = 0.01 (two-sided) to demonstrate statistically significant difference between TransCon PTH and placebo. Taking into account of approximately 10% dropout, a total sample size of 76 is targeted.

15.5. SIGNIFICANCE

Statistical significance is defined as $P < 0.05$ (2-Sided).

15.6. ACCOUNTABILITY

Subjects with missing data, including missed assessments and early discontinuation will be summarized.

15.7. DEVIATION REPORTING

Major protocol deviations will be summarized.

15.8. UNBLINDING PROCEDURES

The Investigator and site personnel will remain blinded to the randomization code during the trial. Treatment assignment for an individual subject should be unblinded by the Investigator only in an emergency (e.g., event concerning subject safety) and only if knowledge of the treatment assignment is urgently needed for the clinical management or welfare of the subject. The investigator is encouraged to notify the Medical Monitor or clinical program manager before unblinding, when possible, but priority should be given to treatment of the subject.

The Investigator must record the date and reason for revealing the blinded treatment assignment for that subject within the IRT. Treatment assignment may be unblinded by the Sponsor to satisfy expedited safety reporting requirements of regulatory authorities. The system to unblind an assignment will be maintained and executed through the IRT, which will be available 24 hours a day, 7 days a week.

16. TRIAL CONDUCT

16.1. SITE INITIATION

Prior to participation, investigational sites and investigators will be evaluated for appropriate qualifications and ability to execute the trial. Each investigational site must undergo appropriate training on the trial protocol and ancillary trial procedures and documents through participation in a Site Initiation Visit (SIV) or an Investigator Meeting (IM). Protocol and GCP training must take place before any subjects are enrolled at a site. SIVs and IMs will include, but may not be limited to, study drug preparation and administration procedures, data collection requirements, and subject eligibility requirements.

16.2. DATA HANDLING AND RECORD KEEPING

16.2.1. Collection of Data

Data will be collected in the eCRF. The eCRF is an integral part of the trial and subsequent reports. It must be used to capture trial-specific data collected and must be kept current to reflect subject status during the course of the trial. Only a Subject Identification Number will be used to identify the subject. The investigator must keep a separate Subject Identification Code List with subject names and medical record numbers (or other personal identifiers).

The trial will use an Internet-based remote data entry system to collect clinical trial data at the investigational sites. The system complies with 21 CFR Part 11 and ICH E6 (R2) GCP. The system will be used to enter, modify, maintain, archive, retrieve, and transmit data. The system is configured based on the requirements from the Sponsor. Source documents are to be retained to enable a reconstruction and evaluation of the trial. Source documents include the site files and trial worksheets provided by the Sponsor. Data will be recorded in the trial worksheets as appropriate to complete and/or clarify the source data.

The design of the computerized system complies with all the applicable regulatory requirements for record keeping and record retention in clinical trials [21 CFR Part 11 and ICH E6 (R2) GCP] to the same degree of confidence as is provided with paper systems. Clinical investigators must retain either the original or a certified copy of all source, including query resolution correspondence. The system is designed so that changes to any record do not obscure the original information. The audit record clearly indicates that a change was made and clearly

provides a means to locate and read the prior information. All changes to the data have an electronic audit trail, in accordance with 21 CFR 11.10(e). Electronic signatures will be used in conformance with 21 CFR Part 11.

16.2.2. Coding Dictionaries

Concomitant medications entered into the database will be coded using the WHO Drug Reference List, which employs the Anatomical Therapeutic Chemical classification system. Medical history for illnesses and AEs will be coded using the medical dictionary for regulatory activities (MedDRA).

16.2.3. Data Handling

eCRFs should be completed in a timely manner to enable the sponsor or designee to perform central monitoring of data. Subsequent to data entry, a study monitor may perform source data verification within the EDC system. Original entries as well as any changes to data fields will be stored in the audit trail of the system. Prior to database lock, the investigator will use his/her log in credentials to confirm that the forms have been reviewed, and that the entries accurately reflect the information in the source documents. The eCRF captures the data required per the protocol schedule of events and procedures. System-generated or manual queries will be issued to the investigative site staff as data discrepancies are identified by the monitor or sponsor, who routinely review the data for completeness, correctness, and consistency. The site is responsible for responding to the queries in a timely manner, within the system, either by confirming the data as correct or updating the original entry, and by providing the reason for the update (e.g., data entry error). At the conclusion of the trial, Sponsor will provide the site with a read-only archive copy of the data entered by that site. This archive must be stored in accordance with the records retention requirements outlined in Section 16.2.1.

16.2.4. Direct Access to Source Data/Documents

The investigator/trial site is to provide direct access to source data/documents for trial-related monitoring, audits, IRB/EC review, and regulatory inspection.

16.2.5. Record Keeping

The investigator is responsible for maintaining adequate records to fully document the conduct of the trial consistent with that noted in ICH E6 (R2), including but not limited to the following:

1. All versions of the Investigator's Brochure
2. Signed Protocol and Amendments in effect during the conduct of the trial
3. Signed ICFs
4. Source documents, including adequate case histories, questionnaires, and subject diaries
5. Signed, dated, and completed eCRFs and documentation of data corrections
6. Notification of SAEs and related reports
7. Dated and documented IRB/EC approvals and approval by regulatory authorities, as required
8. Normal laboratory values

9. Laboratory certifications
10. Curricula Vitae of all clinical investigators
11. Completed Forms FDA 1572, as applicable
12. SIV documentation
13. Delegation of Authority Log
14. Subject Screening & Enrollment Log(s)
15. Subject Identification Code List
16. Study drug accountability documentation
17. Signed agreements between involved parties
18. Relevant communication, including that related to monitor site visits (e.g., letters, meeting notes, notes from telephone calls)
19. Interim, annual, or final reports to IRBs/ECs and regulatory authorities, as required
20. Audit certificate(s), if applicable

16.3. DATA QUALITY CONTROL

16.3.1. Monitoring Procedures

The Sponsor and/or its representative may make periodic visits to the investigational site to assess compliance with trial procedures and regulatory requirements; to ensure that the safety, welfare, and privacy of subjects are being protected; and to verify the accuracy and integrity of the trial data. In addition, independent Quality Assurance site audits may be conducted as verification of the quality and compliance of trial conduct.

The Sponsor and/or its representative will periodically review the trial data to ensure that data are being appropriately collected and reported. Queries and corrections will be made as needed.

16.3.2. Data Management

Sponsor or designee will be responsible for activities associated with the data management of this trial. The standard procedures for handling and processing records will be followed per GCP and Sponsor and/or CRO's standard operating procedures (SOPs). A comprehensive data management plan will be developed including a data management overview, database development, validation and maintenance, data entry and processing, external data transfer, data validation and archive, and medical coding processes. Trial site personnel will be responsible for providing resolutions to all data queries. The investigator will be required to document electronic data review to ensure the accuracy of the corrected and/or clarified data.

16.4. AUDITING PROCEDURES

In addition to the routine monitoring procedures, a GCP Quality Assurance audit may be initiated by the Sponsor. The investigator has to ensure that subjects/parents/legal guardians are aware of and consent to personal information being reviewed during the data verification process as a part of monitoring/auditing/inspection by the Sponsor, properly authorized agents of the Sponsor, or competent authorities. In addition, participation and personal information is treated

as strictly confidential to the extent that applicable law permits and to which it is not publicly available. The purpose of audits and inspections is to evaluate compliance with the principles of GCP, international and local regulatory requirements, and the trial protocol. The audit or inspection may include, for example, a review of all source documents, drug records, original clinic medical notes, and some or all of the facilities used in the trial.

The audits may be conducted by the Sponsor or Sponsor's selected agent in accordance with Sponsor's SOP or SOPs of the selected and properly authorized agent. A competent authority may also wish to conduct an inspection during the trial or after its completion. If an inspection is requested by a competent authority, the investigator must inform the Sponsor immediately that this request has been made. The investigator and his/her institution will permit all monitoring, audits, and regulatory inspections, providing direct access to source data.

16.5. LABORATORY QUALITY STANDARDS

Laboratory tests or evaluations described in this protocol will be conducted in accordance with quality laboratory standards as described in the SOPs of the local and central laboratories. Some blood samples may be used for laboratory test validation.

The laboratories will provide a list of reference ranges for applicable analyses before trial start. These will be held in the investigator site file and the trial master file. The methods employed for each assay should be available upon request. Any change in the laboratory procedures, reference values, etc., during the trial must promptly be communicated to the Sponsor. The laboratories may also be audited by the Sponsor or by competent authorities.

16.6. TRIAL TERMINATION OR COMPLETION

The investigator should notify the IRB/EC in writing of the completion or early termination of the trial. End of trial (EOT) is defined as last subject last visit.

Upon trial completion or termination, applicable regulatory reporting requirements will be followed. The Sponsor reserves the right to terminate the trial at any time for any reason including insufficient efficacy and unanticipated safety concerns. If the trial is prematurely terminated, the investigator should promptly inform the subjects and ensure appropriate therapy and follow-up.

The Sponsor may stop this trial at a particular site for any of the following reasons:

- The site cannot enroll an adequate number of subjects
- Serious and/or persistent non-compliance with the protocol or clinical trial conduct
- Careless or premeditated false documentation in the eCRF
- Inadequate cooperation with the investigator
- Non-compliance with GCP and/or regulatory requirements
- The investigator requests discontinuation

The Sponsor must also terminate the trial prematurely for any of the following reasons:

- Unjustifiable risk and/or toxicity in risk-benefit analysis (occurrence of new adverse events unknown to date in respect of their nature, severity, duration or frequency in relation to the current established safety profile of the study drug)
- New scientific evidence becomes available during the study that could affect the subject's safety

16.7. CHANGES TO THE PROTOCOL

Changes in any portion of this protocol must be documented in the form of an amendment from the Sponsor and must be approved by the investigational site's IRB/EC and regulatory authorities, as required, before the amendment is implemented. However, in the event of apparent immediate hazard to a subject, a deviation from the protocol is allowed in order to eliminate the hazard. In this case, the deviation and the reason for it must be reported as required by regional regulations to the applicable IRB/EC and regulatory authorities, along with a proposed protocol amendment if appropriate.

Protocol amendments may only be made with prior written approval of the Sponsor and/or its representative and documented approval or favorable opinion from applicable regulatory authorities or regional IRB/EC, as required. The investigator must send a copy of the documented approval to the Sponsor and/or its representative.

16.8. OTHER CHANGES IN TRIAL CONDUCT

Changes in trial conduct are not permitted. Any unforeseen changes in trial conduct will be recorded in the clinical study report.

16.9. CLINICAL STUDY REPORT

Data will be reported in a clinical study report in compliance with requirements of the current version of ICH E3. A signatory investigator will review and sign the clinical trial report. The signatory coordinating investigator(s) for the clinical study report will be selected based on experience and knowledge in clinical trials, treatment of HP and involvement in this trial.

16.10. USE OF INFORMATION AND PUBLICATION

The data and information generated in this trial are the exclusive property of the Sponsor and are confidential. Written approval from the Sponsor is required prior to disclosing any information related to this trial. Publication of the results will be based on appropriate analyses and review of the complete data. Authorship will be determined based on enrollment of eligible subjects or contribution to the design, conduct, or interpretation of the trial. Publication of any data of this trial without prior Sponsor approval is not permitted.

17. ETHICAL AND LEGAL CONSIDERATIONS

This trial will be conducted in accordance with the following:

- Protocol-related and trial-related documents
- GCPs as outlined in ICH E6 (R2) and regional regulations

- Declaration of Helsinki
- Regional required subject data protection laws and regulations
- Applicable regional regulations
- US Federal Regulations, as applicable

17.1. DATA MONITORING COMMITTEE

Independent oversight of this trial will be provided by a DMC. Its duty is to regularly review the progress of the trial and assess the accumulating safety data. After each meeting it will advise the Sponsor on the continuing safety of current subjects in the trial and on the continuing validity and scientific merit of the trial. All decisions about the conduct of the trial will rest solely with the Sponsor. The DMC will consist of members, all with experience in clinical studies, and who will operate based on the Charter agreed upon. The Charter will define data content, format, and review frequency. The Sponsor may attend the DMC meetings.

17.2. INFORMED CONSENT

The ICF must be reviewed by the Sponsor and/or its representative prior to submission to a regional IRB/EC for approval. A copy of the ICF approved by the review board must be forwarded to the Sponsor and/or its representative.

The ICF (and Subject Information Sheet, if applicable) documents the trial-specific information the investigator provides to the subject and the subject's agreement to participate. The investigator or designee will fully explain in layman's terms the nature of the trial along with the aims, methods, anticipated benefits, potential risks, and any discomfort participation may entail. The ICF and Subject Information Sheet must be appropriately signed and dated before the subject undergoes any trial-related procedure. The original and any amended signed and dated ICFs and subject information sheets must be retained at the trial site with a copy of each provided to the subject.

17.3. INSTITUTIONAL REVIEW BOARD/ETHICS COMMITTEE APPROVALS

The Principal Investigator (PI) at each site is responsible for obtaining approval from the appropriate regional IRB/EC for the final protocol, Sponsor-approved ICF and subject information sheet (if applicable), and any advertisements to recruit subjects. Written approval of these documents must be obtained from the committee before any subject is enrolled at a trial site.

The PI is also responsible for the following interactions with the regional IRB/EC:

1. Obtaining review board approval for any protocol amendments and ICF revisions before implementing the changes
2. Providing the review board with any required information before or during the trial
3. Submitting progress reports to the review board as required during the conduct of the trial, requesting re-review and approval of the trial as needed, and providing copies of all review board re-approvals and relevant communication to the Sponsor and/or its representative

4. Notifying the review board of all serious and unexpected AEs related to the study drug reported by the Sponsor and/or its representative, as required
5. Notifying the review board of the end of trial participation, in accordance with regional guidelines and regulations

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19. SIGNATURE OF AGREEMENT

In signing this protocol, the investigator agrees to:

- Conduct the trial in accordance with the relevant, current protocol and make changes only after notifying the Sponsor or its representative, except where necessary to eliminate apparent immediate hazards to human subjects
- Comply with the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use Guideline on Good Clinical Practice plus appropriate regional regulatory laws and requirements
- Personally conduct or supervise the described investigation
- Inform any subjects or persons used as controls that the study drugs are being used for investigational purposes
- Ensure requirements relating to obtaining informed consent and regional ethical or institutional review board approval have been met
- Report to the Sponsor or its representative any adverse events that occur in the course of the investigations, as specified in Section 12
- Read and understand the Investigator's Brochure, including potential risks and side effects of the study drug
- Ensure all associates, colleagues, and employees assisting in the conduct of the trial are informed of their obligations in meeting their commitments
- Maintain adequate and accurate records and make these available for inspection by the Sponsor and/or its representative or any regulatory agency authorized by law
- Promptly report to the regional ethical or institutional review board all changes in research activity and all unanticipated problems involving risks to human subjects or others
- Comply with all other requirements regarding the obligations of clinical investigators and all other pertinent requirements
- Administer study drug only to subjects who meet trial entry criteria and are enrolled in the trial and only according to the guidelines set forth in this protocol
- Sign a Form 1572, as applicable

SIGNATURE OF AGREEMENT

I have read and understand the information in this clinical trial protocol, including the potential risks and side effects of the study drug, and agree to personally conduct or supervise the described investigation(s) in accordance with the relevant, current protocol(s) and will not deviate from the protocol, except when necessary to protect the safety, rights, or welfare of subjects. I agree to inform all subjects that the study drug is being used for experimental purposes, and I will ensure that the requirements related to obtaining informed consent are met. I agree to report to the Sponsor any adverse events that occur in the course of the investigation(s).

1. I agree to ensure that all associates, colleagues, and employees assisting in the conduct of the trial are informed about their obligations in meeting the above commitments
2. I will not make any changes in the research without IRB/EC approval, except where necessary to eliminate apparent immediate risks to human subjects
3. I agree to maintain all information in this document and regarding the study as confidential and to use it only for the purpose of conducting the study. I agree not to forward this document to any third party without the prior written authorization of the Sponsor

Investigator:

Printed Name and Title: _____

Signature: _____

Date: _____

20. APPENDICES

APPENDIX 1. CONTRACEPTION

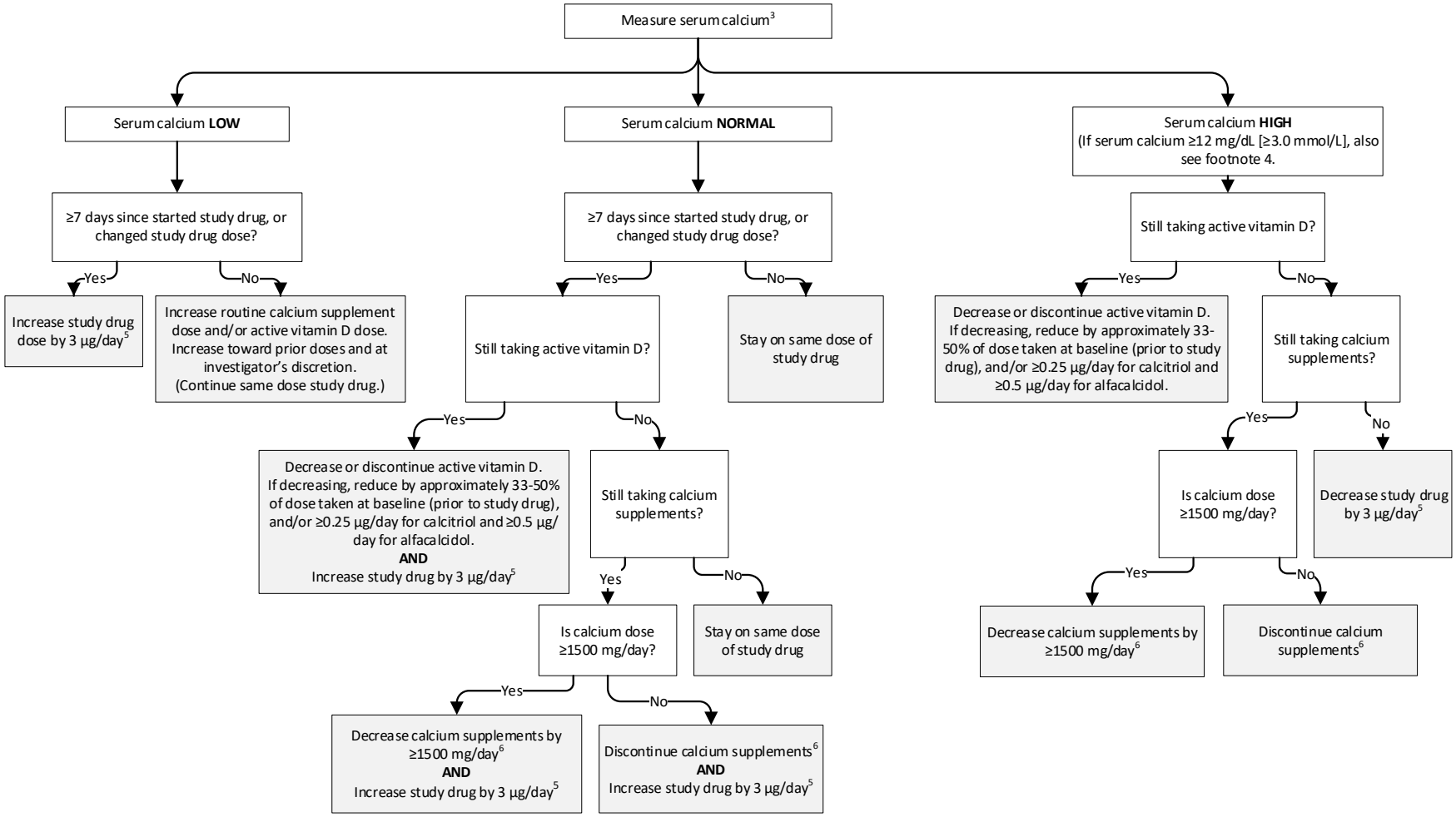
Highly effective contraception are methods that can achieve a failure rate of less than 1% per year when used consistently and correctly, following the CTFG 2014 recommendations, such methods include:

- Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation:
  - Oral
  - Intravaginal
  - Transdermal
- Progestogen-only hormonal contraception associated with inhibition of ovulation:
  - Oral
  - Injectable
  - Implantable
- Intrauterine device (IUD)
- Intrauterine hormone-releasing system (IUS)
- Bilateral tubal occlusion/ligation
- Vasectomized partner
- Sexual abstinence, defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments
- Postmenopausal. A postmenopausal state is defined as no menses for 12 months without an alternative medical cause

Methods of contraception with a failure rate of more than 1% per year with consistent adherence are not permitted for female participants of childbearing potential. Periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhoea method (LAM) are not acceptable methods of contraception.

APPENDIX 2. TITRATION ALGORITHM

Titration Algorithm[1]: Study Drug[2], Active Vitamin D, and Calcium Supplements (Goal to Gain Independence from Conventional Therapy)



[1] At Visit 1 (Week 0, Day 1), start study drug at 18 µg/day and decrease active vitamin D dose by 33-50% (e.g., skip second dose of the day if taking BID, and skip final dose of the day if taking TID).
[2] *Study drug* refers to TransCon PTH or placebo.
[3] *sCa* refers to either albumin-adjusted sCa and/or ionized calcium. For the purposes of this trial, the normal ranges are: albumin-adjusted sCa 8.3-10.6 mg/dL (2.07-2.64 mmol/L); ionized calcium 1.16-1.32 mmol/L.
[4] If albumin-adjusted sCa ≥12.0 mg/dL (3.00 mmol/L) or ionized calcium ≥1.50 mmol/L, hold study drug for approximately 2-3 days. Remember to resume study drug therapy afterwards. Also reduce study drug, active vitamin D, or calcium as per algorithm.
[5] Check sCa within 7-14 days after any changes in study drug dose; standing calcium, standing vitamin D doses; or sCa outside the normal range. A scheduled visit or LV within 7-14 days meets this requirement. When scheduled study visits occur less frequently (e.g. 13 weeks apart) then an ULV should be pursued.
[6] The goal is to demonstrate independence from therapeutic doses of calcium supplements. In case needed to meet recommended dietary intake of calcium, it is permitted to take calcium supplements ≤600 mg/day as a nutritional supplement for the sake of reaching the recommended dietary intake.

Notes:
Adjustments of study drug, calcium and/or active vitamin D will be made per the titration algorithm based on the results of the most recent laboratory results whether scheduled or unscheduled. When central and local calcium values are obtained concurrently, local values should be used to guide titration.
At all times during the trial, subjects with **symptoms** of hyp**o**calcemia may take **PRN doses** of calcium (preferred) and/or active vitamin D, and/or do an ULV visit to **measure sCa**. Subjects with **symptoms** of hyp**er**calcemia may **hold doses of study drug** for 1 day and/or do an ULV to **measure sCa**. An ULV must be performed within 7 days of a PRN supplement dose or a held dose. If due to symptoms >2 PRN doses of SoC are taken or >2 doses of SoC and/or study drug are held within those 7 days, an ULV is required within 2 days of the third PRN or held dose.

APPENDIX 3. SCHEDULE OF EVENTS

Period	**Screening** ***Supplement Optimization***	**Blinded Treatment Period and Start of OLE**												
Visit	**Screening**[1]	**V1**	**LV1**	**LV2**	**V2**	**LV3**	**V3**[2]	**V4**[2]	**V5**[2]	**V6**	**V7**[2]	**V8**[2]	**V9**	**V10**[3]**/ET**[4]
Week	-6 to -2	0	0	1	2	3	4	6	8	10	12	16	20	26
Day	-42 to -14	1	3	8	15	22	29	43	57	71	85	113	141	183
Window			+1 day		+2 days			± 2 days			± 3 days			
Informed consent	X													
COAs[5]	X	X								X			X	X[6]
Demographics	X													
Height, weight measurements	X													
Vital sign measurements[7]	X	X[8]			X		X	X	X	X	X	X	X	X[9]
Medical history	X													
Prior & Concomitant medication	X	X			X		X	X	X	X	X	X	X	X
Physical examination	X	X									X			X
12-lead ECG[10]	X													
DXA[11]	X													X[12]
X-ray of non-dominant wrist and left hand[13]	X													
24-hour urine collection[14]	X[14]	X[14]									X[14]			X[14]
Urine collection for local lab assessments[15]	X	X												
Blood collection for local lab assessments[16]	X[17]		X	X	X	X	X	X	X	X				
Blood collection for central lab	X	X			X		X	X	X	X	X	X	X	X
Dietary calcium questionnaire[18]	X	X												X
Subject diary activation and training	X													
Subject diary review		X			X		X	X	X	X	X	X	X	X
HP-related therapy optimization[19]	X													
SoC titration[20]		X	X	X	X	X	X	X	X	X	X	X	X	X[20]

Period	**Screening** ***Supplement Optimization***	**Blinded Treatment Period and Start of OLE**												
Visit	**Screening**[1]	**V1**	**LV1**	**LV2**	**V2**	**LV3**	**V3**[2]	**V4**[2]	**V5**[2]	**V6**	**V7**[2]	**V8**[2]	**V9**	**V10**[3]**/ET**[4]
Week	-6 to -2	0	0	1	2	3	4	6	8	10	12	16	20	26
Day	-42 to -14	1	3	8	15	22	29	43	57	71	85	113	141	183
Window			+1 day		+2 days			± 2 days			± 3 days			
Treatment assignment	X[21]													X[22]
Study drug training		X												
Study drug dispensing		X			X		X	X	X	X	X	X	X	X
Study drug receipt & compliance review					X		X	X	X	X	X	X	X	X
Adverse event review[23]		X			X		X	X	X	X	X	X	X	X
On site study drug administration		X[24]												X[25]
Local tolerability assessment		X[26]												X[27]
CCI [redacted]		X			X					X				X
TransCon PTH/placebo titration[28]				X	X	X	X	X	X	X	X	X	X	X

[1] Following randomization, it is recommended to start Visit 1 within 2 weeks from the time of randomization.

[2] In selected countries, home/virtual visits can be performed instead of on-site visits at Visit 3, 4, 5, 7 and 8.

[3] Visit 10 marks the end of the Blinded Treatment Period. Subjects still taking active vitamin D, or subjects off active vitamin D and taking study drug ≥ 30 µg/day entering this visit will start open-label TransCon PTH at a dose of 18 µg/day, with the 1st dose taken in clinic on Visit 10. Subjects off active vitamin D and taking study drug < 30 µg/day will start TransCon PTH at the same dose of study drug taken at the end of the Blinded Treatment Period (Exception: in cases of out-of-range sCa level at Visit 10, adjust the TransCon PTH dose and/or calcium doses as per Figure 8 and Appendix 2).

[4] Early Termination (ET) Visit for the Subjects who discontinue the trial prior to Visit 10. The structure and assessments of this ET visit should be as similar as possible to Visit 10.

[5] COAs: PRO measures must be completed by the subject without assistance and prior to conducting any clinical assessments or supplement dose adjustments. On visit 6, 9 and 10/ET, additional CCI [redacted] needs to be completed by the subject. The CGI-S should be completed by the investigator after all clinical assessments are completed.

[6] In selected English speaking countries/sites, approximately 2 weeks prior to Visit 10, subjects will be contacted to set up a one-hour phone interview to occur within 2 weeks after Visit 10 to discuss their experience in the trial. Additionally, in case of subject discontinuation before or at Visit 10, the phone interview will be scheduled to be completed within 2 weeks after the early termination visit. The phone interview will be conducted by an external vendor, and not by the site or the sponsor.

[7] Subject should rest for at least 5 minutes before vital sign measurements, including respiratory rate, temperature, orthostatic BP and heart rate. BP and heart rate are performed while the subject is sitting. The subject is then asked to stand up, within 2 minutes of doing so, BP and heart rate are measured again.

[8] Orthostatic BP and heart rate should also be performed 30 minutes after study drug administration.

[9] Orthostatic BP and heart rate should also be performed 30 minutes after study drug administration only for subjects still taking active vitamin D or subjects off active vitamin D and taking study drug ≥ 30 µg/day at the end of the Blinded Treatment Period.

[10] Standard ECG must include QT interval and Heart Rate.

[11] A historical DXA may be utilized if it was performed within 6 months prior to Screening and report includes required elements per Section 11.7.

[12] A DXA is performed at or within one week prior to Visit 10.

[13] An X-ray of the non-dominant wrist and hand with evidence of epiphyseal closure is only required for subjects who are ≤ 25 years old as of Screening. A historical X-ray may be utilized.

[14] 24-hour urine collection is performed within 52 weeks prior to Screening or during the Screening Period. After the investigator has confirmed the subject is eligible to move into the Blinded Treatment Period, 24-hour urine collection is performed within one week prior to Visit 1. The subject should also perform this collection at home within one week prior to Visit 10 while the subject could perform this collection at home within one week (+/- one week) of Visit 7.

[15] Only for female subjects of childbearing potential.

[16] Local lab assessments may always be performed at investigator's discretion e.g. for symptoms or to guide SoC or TransCon PTH/placebo titration if necessary, at any visits after Visit 6 during Blinded Treatment Period, or at any point in time as needed.

[17] Multiple local laboratory assessments over the approximate 4 weeks of the Screening Period are expected in order to optimize both the albumin-adjusted or ionized sCa to the normal range, as well as normalize the sMg and vitamin D level. Repeat TSH may be performed during the Screening Period if the baseline measurement is out of the allowable range.

[18] Based on review of dietary calcium questionnaire, subjects will be counseled to maintain a stable dietary calcium and to avoid unnecessary/excessive dietary sodium intake throughout the trial.

[19] During Screening, HP-related therapies (calcitriol, alfacalcidol, calcium, magnesium, and vitamin D3) will be optimized to achieve the protocol-specified ranges for sCa, 25(OH) vitamin D, and sMg. See Section 9.5.1.

[20] See Section 9.5.2.1, Section 9.5.3.1 (for Visit 10) and Appendix 2.

[21] Randomization may occur only after Medical Monitor or designee confirmation of eligibility.

[22] See Section 9.4.2. At Visit 10, subjects still taking active vitamin D or subjects off active vitamin D and taking study drug ≥ 30 µg/day will start TransCon PTH at a dose of 18 µg/day while subjects off active vitamin D and taking study drug < 30 µg/day will continue their TransCon PTH dose taken at the end of the Blinded Treatment Period (Exception: in cases of out-of-range sCa level at Visit 10, adjust the TransCon PTH dose as per Appendix 2).

[23] Adverse event review includes questions about general well-being, changes to health or medications, hypo- or hypercalcemic symptoms, vasodilatory symptoms as AESI, emergency/urgent care visits or hospitalizations, and abnormal results from physical examination, examination of injection sites, and laboratory results, as applicable.

[24] On-site drug administration to include on-site observation for at least 30 minutes for local tolerability assessment and adverse reactions, including light headedness.

[25] On-site drug administration only for subjects still taking active vitamin D at Visit 10 or subjects off active vitamin D and taking study drug ≥ 30 µg/day entering Visit 10.

[26] Local tolerability assessment including redness, itching, swelling and pain assessment to be performed at Visit 1 at time of the first study drug injection and at least 15 minutes post dose.

[27] Local tolerability assessment including redness, itching, swelling and pain assessment to be performed at Visit 10 only for subjects still taking active vitamin D at Visit 10 or subjects off active vitamin D and taking study drug ≥ 30 µg/day entering Visit 10, at time of the study drug injection and at least 15 minutes post dose.

[28] See Section 9.5.2.2, Section 9.5.3.2 and Appendix 2.

Period	**Extension**														
Visit	**LV4**[1]	**LV5**[1]	**V11**	**LV6**[1]	**LV7**[1]	**LV8**[1]	**V12**	**V13**[2]	**V14**[2]	**V15**[2]	**V16**	**V17**[2]	**V18**	**V19 to V25**[2]	**V26 (EoT)/ET**[3]
Week	26	27	28	29	30	32	34	38	42	46	52	65	78	91 to 169[4]	182
Day	185	190	197	204	211	225	239	267	295	323	365	456	547	638 to 1184	1275
	2-3 days post-V10	7-8 days post-V10	14-16 days post-V10	21-23 days post-V10	28-30 days post-V10	±2 days			±3 days		±7 days				
COAs[5]							X				X		X	X[6]	X
Vital sign measurements[7]			X				X	X	X	X	X	X	X	X[8]	X
Concomitant medication review			X				X	X	X	X	X	X	X	X[9]	X
Physical examination								X			X		X	X[10]	X
Weekly diary dispensing								X							
Subject diary review			X				X	X	X	X	X	X	X		
Blood Collection for local lab assessment[11]	X	X	X	X	X	X	X	X	X						
Blood collection for central lab assessments			X		X		X	X		X	X	X	X	X[12]	X
24-hour urine collection											X[13]			X[13]	X[13]

Period	**Extension**														
Visit	**LV4**[1]	**LV5**[1]	**V11**	**LV6**[1]	**LV7**[1]	**LV8**[1]	**V12**	**V13**[2]	**V14**[2]	**V15**[2]	**V16**	**V17**[2]	**V18**	**V19 to V25**[2]	**V26 (EoT)/ET**[3]
Week	26	27	28	29	30	32	34	38	42	46	52	65	78	91 to 169[4]	182
Day	185	190	197	204	211	225	239	267	295	323	365	456	547	638 to 1184	1275
	2-3 days post-V10	7-8 days post-V10	14-16 days post-V10	21-23 days post-V10	28-30 days post-V10	±2 days			±3 days		±7 days				
DXA											X[14]			X[14]	X[14]
TransCon PTH dispensing			X				X	X	X	X	X	X	X	X	
TransCon PTH receipt & compliance review			X				X	X	X	X	X	X	X	X	X
Adverse event review[15]			X				X	X	X	X	X	X	X	X[9]	X
SoC titration[16]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
TransCon PTH titration		X	X	X	X	X	X	X	X	X	X	X	X	X	

[1] LV4-LV8 are performed for subjects who are still taking active vitamin D at Visit 10 or subjects off active vitamin D and taking TransCon PTH/placebo dose ≥30 µg/day entering Visit 10.
[2] In selected countries, home/virtual visits may be performed at Visits 13, 14, 15, 17, 19, 21, 23, and 25.
[3] Early Termination (ET) Visit for the subjects who discontinue the trial after Visit 10. The structure and assessments of the ET visit should be as similar as possible to Visit 26.
[4] Visit 19 to 25 are performed in Week 91, 104, 117, 130, 143, 156 and 169.
[5] COAs: PRO measures must be completed by the subject without assistance and prior to conducting any clinical assessments. The CGI-S should be completed by the investigator after all clinical assessments are completed.
[6] COAs will be completed at Visits 20, 22, 24.

[7] Subject should rest for at least 5 minutes before vital sign measurements, including respiratory rate, temperature, orthostatic BP and heart rate. BP and heart rate are performed while the subject is sitting. The subject is then asked to stand up, within 2 minutes of doing so, BP and heart rate are measured again.
[8] Vital sign measurements are performed at Visit 20, 22 and 24.
[9] Correspondence (e.g., telemedicine, phone call, email) with subject is required to perform concomitant medication review, including PRN doses of SoC, and adverse event review if visit is not performed on-site.
[10] Physical Examination is performed at Visit 20, 22 and 24.
[11] Local lab assessments may be performed at the clinic visits, or at any time at the investigator's discretion e.g., for symptoms or to guide SoC or TransCon PTH titration.
[12] Blood Collection for central lab assessments only at Visit 19, 20 and every other visit after.
[13] 24-hour urine collection is performed by the subject at home within one week (+/- one week) of Visit 16, 20, 24, and within one week prior to Visit 26.
[14] DXA is performed at or within one week (+/- one week) of Visit 16, 20, and at or within one week prior to Visit 26.
[15] Adverse event review includes a question about general well-being, changes to health or medications, hypo- or hypercalcemic symptoms, vasodilatory symptoms as AESI, emergency/urgent care visits or hospitalizations, and abnormal results from physical examination, examination of injection sites, and laboratory results, as applicable. Two weeks (+ 7 days) after last study drug administration, a telephone contact will take place to evaluate AEs that were ongoing at the final study visit and to evaluate the subject for any further AEs during the 2 weeks since last study drug administration.
[16] See Section 9.5.3.1 and Appendix 2.

APPENDIX 4. SCHEDULE OF LABORATORY ASSESSMENTS

Visit	**Screening**		**1**		**LV1-LV2**	**2**		**LV3**	**3**		**4**		**5**		**6**		**7[1]**	**8-10[1]**
Week	***-6 to -2***		***0***		***0-1***	***2***		***3***	***4***		***6***		***8***		***10***		***12***	***16-26***
Laboratory Type	Local	Central	Local	Central	Local ONLY	Local	Central	Local ONLY	Local	Central	Local	Central	Local	Central	Local	Central	Central	Central
Calcium & Albumin or Ionized Calcium[1]	X	Included in Chem. Panel		Included in Chem. Panel	X	X	Included in Chem. Panel	X	X	Included in Chem. Panel	X	Included in Chem. Panel	X	Included in Chem. Panel	X	Included in Chem. Panel	Included in Chem. Panel	Included in Chem. Panel
25(OH) Vitamin D	X	X		X						X							X	X[2]
1,25$(OH)_2$ Vitamin D		X		X						X							X	X[2]
Chemistry Panel[3]		X		X			X			X		X		X		X	X	X
Hematology Panel[4]		X		X			X			X		X		X		X	X	X
Free PTH[5]				X						X				X			X	X[5]
Antibodies against PTH, TransCon PTH & PEG[6]				X						X				X			X	X[6]
Bone Turnover markers		X		X													X	X[7]
Magnesium	X																	
TSH		X		X						X							X	X[2]
PTH(1-84)		X																

Visit	**Screening**		**1**		**LV1-LV2**	**2**		**LV3**	**3**		**4**		**5**		**6**		**7[1]**	**8-10[1]**
Week	***-6 to -2***		***0***		***0-1***	***2***		***3***	***4***		***6***		***8***		***10***		***12***	***16-26***
Laboratory Type	Local	Central	Local	Central	Local ONLY	Local	Central	Local ONLY	Local	Central	Local	Central	Local	Central	Local	Central	Central	Central
Serum FSH[8]		X																
Urine hCG[9]	X		X[10]															
Serum hCG[9]				X						X				X			X	X
24-hour Urine Panel[11]		X[12]		X[13]													X[12]	X[12]

[1] Local lab assessments may be performed at the clinic visits, or at any time at the investigator's discretion e.g., for symptoms or to guide SoC or study drug titration.
[2] 25(OH) vitamin D, 1,25$(OH)_2$ vitamin D and TSH are assessed at Visit 10.
[3] Including but not limited to: Total Bilirubin, Direct Bilirubin, Indirect Bilirubin, Alkaline Phosphatase, ALT (SGPT), AST (SGOT), GGT, Urea Nitrogen, Creatinine, Uric Acid, Calcium, Phosphate, Total Protein, Albumin, Globulin, CK, Sodium, Potassium, Bicarbonate, Chloride, Magnesium. (At Screening only: also Glucose, Cholesterol and HbA1C [Documented HbA1C result drawn within 12 weeks prior to Screening is acceptable.])
[4] Including but not limited to: Hemoglobin, Hematocrit, RBC, MCH, MCHC, RBC morphology & MCV, WBC, Neutrophils, Lymphocytes, Monocytes Eosinophils, Basophils, Platelets.
[5] Only for subjects at selected sites, where Free PTH assessment will be performed. Free PTH(1-34) and Free PTH(1-33) are assessed at Visit 1, 3, 5, 7 and 10.
[6] Anti-PTH, anti-TransCon PTH and anti-PEG antibodies are assessed at Visit 1, 3, 5, 7 and 10.
[7] Bone turnover markers are assessed at Visit 10.
[8] Follicle stimulating hormone (FSH) is assessed only for female subjects ≥ 45 years old as of Screening, without menses for at least 6 months prior to Screening without an alternative medical cause (e.g., surgically sterile) to determine if they are postmenopausal (i.e., do not require pregnancy testing).
[9] Human chorionic gonadotropin (hCG) (pregnancy test) is assessed only for female subjects of childbearing potential. Female subjects are considered NOT to be of childbearing potential if they are surgically sterile or postmenopausal, defined as age >50 with absent menses for ≥12 months, or age ≥45 years old as of Screening, without menses for at least 6 months prior to Screening and FSH >30 mIU/mL).
[10] Local urine hCG (pregnancy test) results must confirm subject is not pregnant prior to first study drug dose administration at Visit 1.
[11] 24-hour urine panel includes but not limited to: Creatinine, Calcium, Citrate, Uric Acid, Oxalate, Phosphate, Sodium, Potassium, Magnesium, pH and Urine volume, except for 24-hour urine collection within 52 weeks of Screening or during Screening for confirmation of eligibility which only includes Calcium, Creatinine, and urine volume.
[12] 24-hour urine collection is performed by the subject at home within 52 weeks prior to Screening or during the Screening Period, within one week (+/- one week) of Visit 7 and within one week prior to Visit 10.
[13] After the investigator has confirmed the subject is eligible to move into the Blinded Treatment Period, 24-hour urine collection is performed within one week prior to Visit 1.

Period		**Extension Period**												
Visit	**LV4-LV5[1]**	**11**		**LV6[1]**	**LV7[1]**		**LV8[1]**	**12**		**13**		**14**	**15[2]**	**16+[2]**
Week	26-27	28		29	30		32	34		38		42	46	52+
Laboratory Type	Local ONLY	Local	Central	Local ONLY	Local	Central	Local ONLY	Local	Central	Local	Central	Local ONLY	Central	Central
Calcium & Albumin or Ionized Calcium[2]	X	X	Included in Chem Panel	X	X	Included in Chem Panel	X	X		X	Included in Chem Panel	X	Included in Chem Panel	Included in Chem Panel
25(OH) Vitamin D						X					X		X	X[3]
1,25(OH)$_2$ Vitamin D						X					X		X	X[3]
TSH						X					X		X	X[3]
Chemistry Panel[3]			X			X					X		X	X[3]
Hematology Panel[3]			X			X					X		X	X[3]
Antibodies against PTH, TransCon PTH & PEG[4]						X			X		X			X[4]
Bone turnover markers											X			X[5]
Serum hCG						X					X		X	X[6]
24-hour Urine Panel														X[7]

[1] LV4-LV8 are performed only for subjects still taking active vitamin D at Visit 10 or for subjects off active vitamin D and taking TransCon PTH/placebo dose ≥ 30 µg/day at the end of the Blinded Treatment Period.
[2] Local lab assessment may be performed at clinic visits of V15+ or at any time at the investigator's discretion e.g., for symptoms or to guide SoC or TransCon PTH titration.
[3] 25(OH) vitamin D, 1,25(OH)$_2$ vitamin D, TSH, chemistry panel, and hematology panel are assessed at Visit 16 and then every other visit.
[4] Anti-PTH, anti-TransCon PTH and anti- PEG antibodies are assessed at LV7, 12, 13, 16, 17, 18, 19, 20 and every other visit after.
[5] Bone turnover markers are assessed at Visit 16, and every other visit after.
[6] Serum hCG (pregnancy test) is assessed at Visit 16, 17, 18, 19, 20 and every other visit after.
[7] 24-hour urine collection is performed by the subject at home within one week (+/- one week) of Visit 16, 20, 24, and within one week prior to Visit 26.

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